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The Genetic Basis of Various Types of Ichthyosis in a Family Group[1,2]

HELEN OLLENDORFF CURTH AND MADGE T. MACKLIN

Department of Dermatology, College of Physicians and Surgeons, Columbia University, New York, and Department of Medicine, Ohio State University, Columbus, Ohio

VARIOUS TYPES of dyskeratosis occurring in members of a family group of English origin will be described and reasons given for considering the various cutaneous changes as variants of ichthyosis. This discussion will be followed by a genetic analysis of the family-group.

PART I. THE SKIN DISEASE

The study began three years ago with two brothers (pedigree III-25 and III-26) now aged 17 and 15. They were born with rough and blackish skin which covered almost the entire body. The older boy's face and trunk were red at birth and the redness of the face has persisted up to the present time. When he was 15 years old the lesions of the trunk started to fade in summertime and there was evidence of slight perspiration. With colder weather, however, the skin became dark and rough again. The younger brother has lately also shown persistent redness of the face. He has been greatly handicapped by the crippling effect of palmar contractures which have necessitated orthopedic treatment.

The older boy, well developed and intelligent, shows symmetrically distributed thickened verrucous black and hyperkeratotic skin on the hairline, neck, arms, elbows, genitals and the lower extremities from the middle of the thighs downward. Flexor and extensor sides of the lower extremities are about equally involved with slightly greater involvement of the extensor than the flexor surfaces of the upper extremities. The palms show confluent plaques of blackened hyperkeratotic skin resulting in contracture of the hands. Isolated keratoses are found on both soles. There is mild keratosis of the lips, around the mouth, on the ears and on the medial parts of the buttocks. The nipples are transformed into hard, black, keratotic masses. The nails appear normal but are growing rapidly. The younger boy shows cutaneous changes similar to those of his brother (fig. 1). At the age of 14 the younger brother still had

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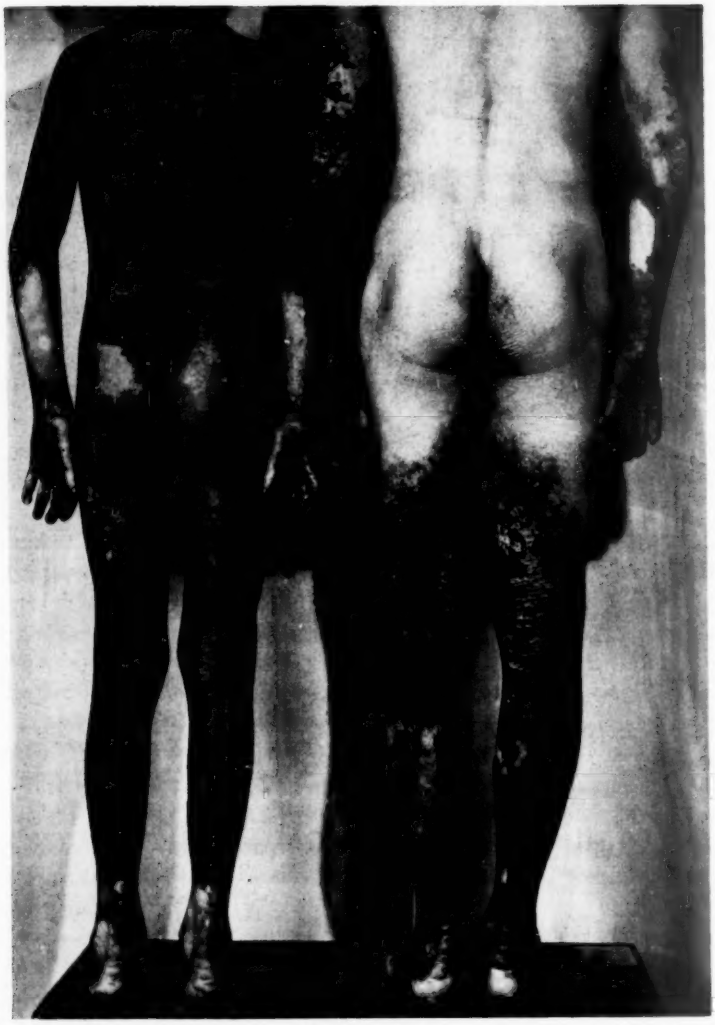

FIG. 1. Back view of the probands, two brothers (III-26 and III-25), aged 15 and 17, suffering from ichthyosis hystrix. Photograph was taken in summer-time when in the older boy the eruption of the trunk with the exception of keratoses of nipples and umbilicus had faded temporarily.

two deciduous lower molars, which subsequently were removed. The second bicuspids erupted late. Since the cutaneous anomaly of these brothers was the most pronounced in the family, it has been designated with a full dark square.

Biopsy of a piece of skin from the older brother (fig. 2) showed a somewhat papillomatous proliferation which had undergone striking hyperkeratosis.

FIG. 2. Biopsy of skin from older brother (III-25) showing ichthyosis hystrix and features reminiscent of epidermodysplasia verruciformis.

The granular layer was greatly disturbed and many of the cells were swollen, appearing hydropic. The keratin just above the kerato-hyalin stratum had a basket weave appearance. Most of the epidermis, which was acanthotic, was edematous. Sweat glands were occasionally dilated with moderate edema of the acini. The normal pattern of the rete had disappeared. The subepidermal cutis revealed a chronic inflammatory reaction. The histologic picture of the lesion suggested an epidermal nevus, a diagnosis which is consistent with ichthyosis hystrix. There were also features reminiscent of epidermodysplasia verruciformis.

Biopsy from the neck of the younger brother showed sections very similar to those of his older brother. Findings were those of an epidermal nevus or ichthyosis hystrix.

We are dealing in the two brothers, therefore, with ichthyosis hystrix, which shows additional clinical features of congenital ichthyosiform erythroderma and in the older brother additional histologic features of epidermodysplasia verruciformis.

The sole cutaneous anomaly of their mother (II-11), one sister (III-27) and some other relatives were keratoses of the elbows and/or knees. The majority of those family members having thin hyperkeratotic plaques (fig. 3) were females but one male member (III-8) exhibited thick, verrucous masses

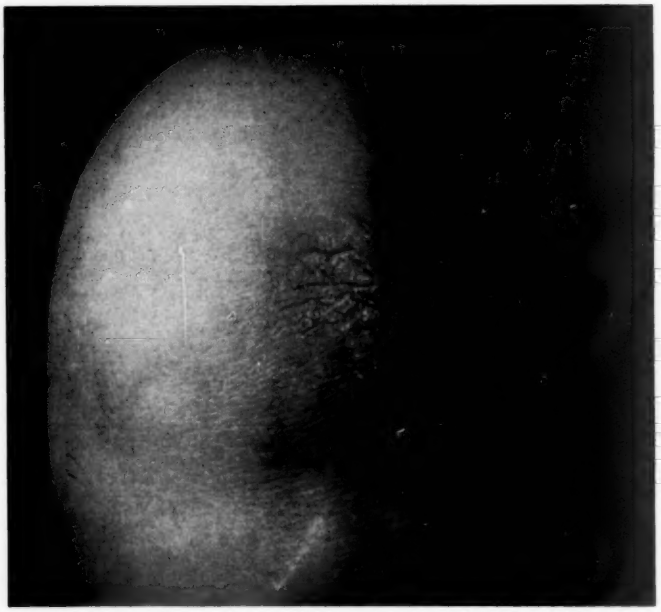

FIG. 3. Mild keratosis of right knee of probands' aunt (II-3). The left knee was similarly involved.

FIG. 4. Thick keratoses of knees and patellas of male cousin (III-8) who also had palmar keratoses.

over the knees, patellas (fig. 4) and elbows. The symbol for the keratoses of elbows and/or knees is a quarter dark square in the lower right corner.

Histologic sections of a piece from the hyperkeratosis of the knee of family-member III-8 showed an epidermal nevus or ichthyosis.

Some male relatives (II-5; II-14; III-7 and III-8) had distinctly keratotic palms while female relatives (III-11 and IV-3) had only slightly rough palmar surfaces. It is noteworthy that here again the more severe changes occurred in the male family members. Palmar and/or plantar hyperkeratoses were designated by a quarter dark square in the lower left corner.

Keratosis of the palms is characterized by intense thickening of the horny layer and accentuation of the stratum lucidum.

Almost the entire body of one male cousin (III-7) was covered by large white dry scales of ichthyosis simplex. Since this patient in addition showed keratoses of the elbows, knees, patellas and palms, so that the extent of his dermatosis almost reached the dimensions of ichthyosis hystrix in his cousins, the symbol for his changes is a ¾ dark square. The histologic picture of ichthyosis simplex reveals a marked tendency to cornification.

The maternal grandfather, (I-3) now dead, is said to have had rough dark skin over arms, hands, feet and back. Since his changes were spread over wide areas they were also designated by a ¾ dark square.

Some other family members showed slight degrees of ichthyosis such as rough ankles (V-1) or a discrete verrucous nevus (III-3), malformations or disturbances, not directly connected with ichthyosis, such as polydactylism (IV-15), or allergies in the form of atopic eczema (III-10 and IV-25), dermatitis venenata (II-14) or asthma (IV-18).

Comment

We consider the various cutaneous anomalies shown by members of this kindred as expressions of one basic disturbance, keratinization; however, the extent of the cutaneous manifestations varies in the various family members. Some show localized and others generalized involvement. The long disputed question whether the localized form of ichthyosis ("regional" ichthyosis (Siemens, 1927)) was representative of ichthyosis was finally answered in the affirmative by Bruhns (1912 and 1931) who studied this problem extensively. The localized form of ichthyosis in the family under discussion mainly comprises keratoses of elbows, knees and/or palms while generalized ichthyosis takes the form of ichthyosis simplex or ichthyosis hystrix.

Our concept of regarding the cutaneous changes exhibited by this family as variants of ichthyosis is based on several considerations.

1. There is histologic proof of the same pathogenetic principle governing all the cutaneous changes. They can be classified as showing "accelerated benign dyskeratosis," a concept recently promulgated (Ellis, 1953).

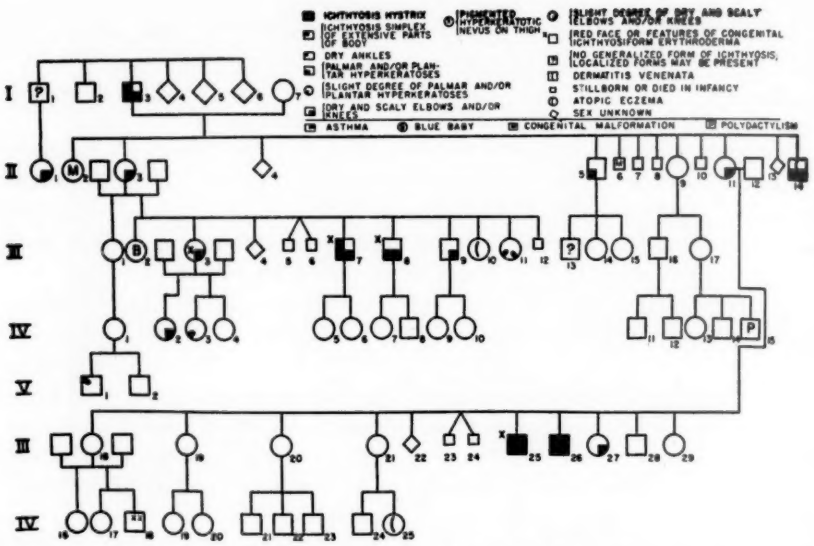

FIG. 5. Pedigree of family W. The probands are III-25 and III-26; their mother is II-11 and their father II-12.

2. Although in the general population these various cutaneous anomalies are rare they occur repeatedly in this family group.

3. The eruptions of the male cousin with ichthyosis simplex and the two probands with ichthyosis hystrix, all three of whom are suffering from the major or generalized forms of ichthyosis, include keratoses of elbows, patellae and palms constituting the minor or localized forms of ichthyosis. Patients showing similar combinations of localized and generalized ichthyosis were also observed by Cohn (1914), Blotevogel (1922), Friedländer (1931), Matras (1933) and others.

4. When examination of families of patients suffering from ichthyosis is extended to many members, the alternate appearance of localized and generalized ichthyosis has occasionally become evident. This phenomenon was documented in a family with 31 members (Hermann, 1951) while we are able to report the result of an investigation of 75 family members (fig. 5). The probands' father (II-12) was Irish. His family being normal was omitted from the pedigree.

The two brothers are suffering from ichthyosis hystrix. In addition, they have shown over trunk and face persistent erythema characteristic of congenital ichthyosiform erythroderma. The brothers, therefore, combine ichthyosis hystrix, a variant of ichthyosis vulgaris, with features of congenital ichthyosiform, erythroderma a variant of ichthyosis congenita. Ichthyosis vulgaris and ichthyosis congenita were previously considered separate entities differing

from each other with regard to localization, age of patient at onset of disease, accompanying signs of inflammation and genetic mechanism. In deciding this issue we find ourselves in full accord with Bruhns (1931) who two decades ago stressed the similarities and transitions between the two types rather than their differences. While noninvolvement of palms and soles seemed to be the rule in ichthyosis vulgaris our patients and those of Gassmann (1904), Fuhs (1924), Ramazzotti (1925) and others showed involvement of these particular sites. Although flexures are usually non-involved in patients with ichthyosis vulgaris involvement of the flexures, such as seen in our patients, seemed to be the rule also in other patients suffering from ichthyosis hystrix (Ramazzotti (1925), Bruhns (1931) and other authors quoted by Bruhns (1931)). It is possible that the severe manifestations of ichthyosis congenita at birth as contrasted with the mild signs of ichthyosis vulgaris in early childhood may have created the impression that ichthyosis congenita is in all cases present at birth and ichthyosis vulgaris is never present in the newborn. However, to reject a case as one of ichthyosis vulgaris for the reason that the dermatosis has been present at birth, appears illogical if one considers ichthyosis vulgaris a genodermatosis.

Previously, the absence or presence of inflammatory signs was considered of differential diagnostic value, ichthyosis vulgaris being free from inflammatory signs and ichthyosis congenita showing considerable signs of inflammation. According to this view the presence of congenital ichthyosiform erythroderma cannot easily be reconciled with the diagnosis of ichthyosis vulgaris. However, Pawlowski (1951) points out that in congenital ichthyosiform erythroderma the erythroderma, which is an inconstant sign of the affection, results from pressure exerted by the thickened keratotic layers and is, therefore, rather an expression of the hyperkeratosis than of any accompanying inflammatory process. It seems obvious that such a reaction in cases of ichthyosis may be present or not but its presence or absence does not seem of sufficient significance for purposes of classifying ichthyosis. Rational and more satisfactory is Winer's (1953) classification of congenital ichthyosiform erythroderma and ichthyosis hystrix, etc. with the epidermal nevi. It will be shown that the pattern of inheritance of our family-group resembles more closely that seen in ichthyosis vulgaris than that observed in ichthyosis congenita.

The histologic picture of the older brother was reminiscent of epidermodysplasia verruciformis, also seen in the histologic pictures of a boy suffering from hystrix-like ichthyosiform erythroderma (Gottron, 1943) and of a girl suffering from bullous ichthyosiform erythroderma and her father suffering from ichthyosis hystrix (Barker and Sachs, 1953).

The younger proband showed hypoplastic teeth, an anomaly which also accompanied the cutaneous changes of the other young male patient suffering from ichthyosis hystrix-like congenital ichthyosiform erythroderma (Gottron,

1943). Other family members had various congenital malformations. II-2 and II-6 were born as blue babies and five other children of generation II were stillborn or died in infancy. Polydactylism was present in IV-15.

Other forms of localized ichthyosis vulgaris occurred as dry ankles, (V-1) and a discrete pigmented hyperkeratotic nevus on the right thigh of a girl (III-3) who also showed dry knees.

Among the family members manifesting signs of ichthyosis only one (II-14) displayed signs of cutaneous allergy. He was suffering from dermatitis venenata. However, several other family members, who did not suffer from ichthyosis (III-10; IV-18 and IV-25) suffered from asthma or atopic eczema. It is doubtful whether in members of this family the incidence of an allergic disposition, especially in those without manifestations of ichthyosis, has any connection with the inherited cutaneous anomaly of ichthyosis. Cockayne (1933) quoting many pedigrees with instances of ichthyosis and associated allergic conditions envisages the possibility that "ichthyosis and the liability to these allergies are due to independent genes lying in the same chromosome and that there is linkage between them."

There was considerable variation of intensity in the keratoses of knees, elbows and palms among male and female family members with the more severe manifestations occurring in the male.

PART II. GENETIC ANALYSIS

1. Evidence that the cutaneous lesions have a genetic basis is seen in the fact that although the condition is rare it is manifesting itself in this family through five generations.

2. Are the cutaneous changes conditioned by a single main gene? There are severe and mild cutaneous manifestations evident in this family. If we consider for a moment the possibility that two different genes are responsible for the two different types of manifestations ichthyosis hystrix may be due to a sex-linked recessive and palmar and plantar keratoses and/or scaly knees and elbows may be caused by another gene which is neither sex-linked nor recessive. The supposition that two separate disease entities are being inherited simultaneously in the family, one a sex-linked recessive, the other, a milder skin disease, appearing in males and females alike, is running counter not only to the tradition of attempting to explain different signs as caused by one basic disease, but also to the laws of probability which would be against two rare dermatoses occurring in the same family. Actually, another pedigree (Hermann, 1951) also shows the alternate occurrence of localized and generalized ichthyosis in successive generations.

If we assume, however, that but one gene with varying expressivity is causing the disorder, all the affected persons would be carrying the same mutant

gene, which, because of modifying factors, one being sex, expresses itself differently in different members of the family.

3. The condition, in this family at least, reaches its fullest expression only in the male. Since we are considering that only one main gene is involved, we believe that thus far in this family complete penetrance has been present only in the males.

4. The main gene is probably a dominant one.

Having presented evidence that the condition is inherited, and having postulated a single main gene, we will consider which of the various modes of transmission the disease exhibits.

A. The gene is not Y borne as in the famous Lambert family (Bett, 1952) in which every person affected with ichthyosis hystrix was a male and was the son of an affected male, and in which all affected males had all their sons affected. In our family group females are exhibiting milder signs of the disease thus ruling out the Y borne mode of transmission.

B. It is not dependent upon a recessive autosomal gene, since although the condition is rare it occurs through four generations in unbroken line of descent in one instance, and through three generations in eight instances, occurrences which are most unlikely to be caused by a recessive gene; furthermore, there is no instance of cousin matings among the parents of affected persons.

C. It is not a sex-linked recessive gene, since an affected father passes it on to affected sons and daughters. The possibility of regarding the manifestations in the females as evidence of the carrier state cannot be considered, since the same degree of manifestation is present in the males who are sons of affected males.

D. and finally the gene behaves in accordance with the dominant mode of transmission being present in approximately half of the total number of offspring who came from matings of one affected with a non-affected parent and being transmitted by males and females to offspring of both sexes. 14 affected children among 35 (after excluding instances of stillbirths or deaths in infancy) denotes involvement of slightly less than 50 per cent which might be explained by incomplete penetrance, especially in the female.

Cockayne (1933) dealing separately with the variants of ichthyosis, since their genetic patterns may differ, nevertheless, finds ichthyosis vulgaris in most cases based on dominant inheritance with a remarkable accent on one sex in many instances. In some pedigrees the male family members escape major involvement; in others there is an excess of male patients; our family group would fall into the latter category. Cockayne (1933) sees the action of a sex-linked modifying gene in families showing an abnormal sex ratio of individuals affected with ichthyosis vulgaris.

Leven (1922) concluded that the inheritance of ichthyosis vulgaris was domi-

nant. Incomplete penetrance and varying expressivity characterize the dominant inheritance pattern of ichthyosis in the family described by us. Similar inheritance patterns were already seen by Wehefritz (1924) who, stressing dominant inheritance, which was neither sex-linked nor sex-limited, remarked on the irregularly dominant pattern and by Gassmann (1904) who emphasized the changing intensity of the manifestations.

A number of cases of ichthyosis vulgaris, quoted by Cockayne (1933), and one reported by Argüelles-Casals (1948), however, seem based on sex-linked recessive inheritance. It should be pointed out, however, that if mild expressions of ichthyosis in family-members were overlooked, inheritance of ichthyosis vulgaris easily assumes the aspect of a sex-linked recessive pattern (Hoede, 1940). If in our study the mild keratoses of the probands' mother and the abortive forms of other family members of generation II would have remained unnoticed, the fact that the probands' grandfather and a male cousin in addition to the probands themselves showed remarkable cutaneous changes would have suggested sex-linked recessive inheritance.

Inheritance of ichthyosis vulgaris in our family of English origin follows the pattern which seems to prevail in families of northern Europe (Cockayne, (1933), and Gates, (1946)).

Kogoj (1950) classifies ichthyosis according to its genetic pattern so that ichthyosis vulgaris, showing dominant inheritance, would belong to one type, and congenital ichthyosiform erythroderma, showing recessive inheritance, to another type of the disorder. Not all cases of ichthyosis, however, conform strictly to the genetic patterns outlined by Kogoj (1950). Moreover, this classification neither allows for the alternate appearance of the variants of ichthyosis in members of a family group (Hermann, (1951), the kindred described in this paper and several other family histories quoted by Cockayne (1933)) nor for atypical pictures of ichthyosis, combining features of variants of ichthyosis, such as seen in male members of the kindred described in this paper, in Wise's (1936) female patient combining features of congenital ichthyosiform erythroderma with palmar and plantar keratoses, in Gottron's (1943) male patient suffering from ichthyosis hystrix-like congenital ichthyosiform erythroderma and in Pellerat and Cariage's (1953) female patient in whom the diagnoses of congenital ichthyosiform erythroderma or ichthyosis vulgaris were considered.

SUMMARY

Two brothers suffering from ichthyosis hystrix showed additional clinical signs of congenital ichthyosiform erythroderma. The older brother had additional histologic features of epidermodysplasia verruciformis. 75 family members were examined and several members were found suffering from various

forms of ichthyosis all based on faulty keratinization. Clinically, the variants could be grouped into localized and generalized forms of ichthyosis, the localized form comprising keratoses of elbows, knees, patellas and palms, and the generalized form appearing as ichthyosis simplex or ichthyosis hystrix. Genetic analysis showed evidence in favor of the concept that the disorder has been conditioned by one main dominant gene which manifested itself with varying degrees of severity in the various family members and with its fullest expression in the male.

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The Correlation Between Parents and Offspring in a Random Mating Population[1]

C. C. LI

Graduate School of Public Health, University of Pittsburgh

IN STUDYING the inheritance of metrical characters in man one of the most useful indices is the correlation between parent and offspring with respect to the character under investigation. This correlation is based upon the measurements of pairs consisting of one parent and one child each. In recent years the author has repeatedly encountered the problem: when both parents and more than one offspring are measured, what sort of correlation should be adopted and what theoretical values would the adopted coefficient have under certain simple conditions. The following is one attempt to generalize the correlation between parent(s) and child(ren) in a random mating population, assuming that the genic effects on the character are additive (that is, the character is measured on an additive scale). Only the correlation due to heredity has been given; that due to environmental factors has been ignored.

CORRELATION BETWEEN PARENTS AND OFFSPRING

Since the product-moment correlation coefficient is independent of units of measurement and origin, it is convenient to assign the values 2, 1, 0, to genotypes AA, Aa, aa, respectively. Also, to facilitate the arithmetic, instead of using the mean value of parents ("mid-parent") and the mean value of children, we use their respective totals. This does not effect the value of the correlation coefficient. The matings $Aa \times Aa$ and $AA \times aa$ will all assume a total value of 2. If there are three children, the sibship (AA, Aa, aa) and (Aa, Aa, Aa) will all assume a total value of 3, and so on. Then we will derive the correlation between the parental total and the offspring total. A theoretical basis for doing this is given in the next section.

The correlation between one parent and one child is too well known to be given here. The correlation table between the sum of two parents and one child may be obtained from the ordinary table of random mating and offspring, such as that used for demonstrating the Hardy-Weinberg Law. Therefore, as examples, we shall give the correlation table between two parents and two children and that between two parents and three children (table 1), where p is the frequency of gene A and q that of a. The corresponding tables for one parent and two or three children may be obtained from table 1 by

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TABLE 1. THE JOINT DISTRIBUTION OF THE SUM OF PARENTAL VALUES AND THE SUM OF CHILDREN'S VALUES IN A RANDOM MATING POPULATION, ASSUMING ADDITIVE GENIC EFFECTS

Two Parents	Two Children in Each Sibship				
	4	3	2	1	0
4	p^4				
3	p^3q	$2p^3q$	p^3q		
2	$\frac{1}{4}p^2q^2$	p^2q^2	$\frac{7}{2}p^2q^2$	p^2q^2	$\frac{1}{4}p^2q^2$
1			pq^3	$2pq^3$	pq^3
0					q^4

	Three Children in Each Sibship						
	6	5	4	3	2	1	0
4	p^4						
3	$\frac{1}{2}p^3q$	$\frac{3}{2}p^3q$	$\frac{3}{2}p^3q$	$\frac{1}{2}p^3q$			
2	$\frac{1}{16}p^2q^2$	$\frac{6}{16}p^2q^2$	$\frac{15}{16}p^2q^2$	$\frac{52}{16}p^2q^2$	$\frac{15}{16}p^2q^2$	$\frac{6}{16}p^2q^2$	$\frac{1}{16}p^2q^2$
1				$\frac{1}{2}pq^3$	$\frac{3}{2}pq^3$	$\frac{3}{2}pq^3$	$\frac{1}{2}pq^3$
0							q^4

TABLE 2. VARIANCE, COVARIANCE, AND CORRELATIONS BETWEEN PARENT(S) AND CHILD(REN) IN A RANDOM MATING POPULATION, ASSUMING ADDITIVE GENIC EFFECTS

		Number of Children in Family				
		$s = 1$ $\sigma_O^2 = 2pq$	$s = 2$ $\sigma_O^2 = 6pq$	$s = 3$ $\sigma_O^2 = 12pq$	$s = 4$ $\sigma_O^2 = 20pq$	general s $\sigma_O^2 = s(s+1)pq$
One Parent	$\sigma_P^2 = 2pq$	$\sigma_{PO} = pq$ $r = \sqrt{\frac{1}{4}}$	$\sigma_{PO} = 2pq$ $r = \sqrt{\frac{2}{6}}$	$\sigma_{PO} = 3pq$ $r = \sqrt{\frac{3}{8}}$	$\sigma_{PO} = 4pq$ $r = \sqrt{\frac{4}{10}}$	$\sigma_{PO} = spq$ $r = \sqrt{\frac{s}{2(s+1)}}$
Two Parents	$\sigma_P^2 = 4pq$	$\sigma_{PO} = 2pq$ $r = \sqrt{\frac{1}{2}}$	$\sigma_{PO} = 4pq$ $r = \sqrt{\frac{2}{3}}$	$\sigma_{PO} = 6pq$ $r = \sqrt{\frac{3}{4}}$	$\sigma_{PO} = 8pq$ $r = \sqrt{\frac{4}{5}}$	$\sigma_{PO} = 2spq$ $r = \sqrt{\frac{s}{s+1}}$

distinguishing the reciprocal crosses and collecting cells according to the genotype of one parent. The variance, covariance, and correlation coefficient of the various cases are given in table 2, in which P stands for parent(s), O for offspring, and s denotes the size of the sibship.

Long-hand calculation is carried up to the case $s = 4$ for one known parent and for two known parents. This leads to the general expression given in the last column of table 2. The correlation between two parents and offspring approaches unity rapidly as the size of sibship increases. That between one parent and offspring, however, approaches $\sqrt{\frac{1}{2}}$ as a limit as s increases indefinitely.

A THEORETICAL BASIS

Now we turn to a more general treatment of the subject. Let x_1 and x_2 be the measurements of father and mother respectively; and let $y_1, y_2, \cdots, y_s$ be the measurements of the s children, y_j being that of the jth child (in order of birth). We are interested in the correlation between the two sets of variates: x_1 and x_2 on one hand, and the $y_1, \cdots y_s$ on the other. Following Hotelling's method (1936), we form a linear expression of each set of variables separately:

$$X = b_1x_1 + b_2x_2, \qquad Y = c_1y_1 + \cdots + c_sy_s,$$

where the b's and c's are constants. The correlation between the two linear expressions, X and Y, depends upon the values of the b's and c's adopted. Hotelling (1936) proposed that the b's and c's should be so chosen that the correlation between X and Y is a maximum. Now, noting that in a random mating population,

$$\sigma^2_{x_1} = \sigma^2_{x_2} = \sigma^2_{y_1} = \cdots = \sigma^2_{y_s} = 2pq;$$
$$\sigma_{x_1x_2} = O; \sigma_{x_iy_j} = pq; \sigma_{y_jy_{j'}} = pq,$$

we obtain

$$\sigma^2_X = 2pq\,(b^2_1 + b^2_2)$$
$$\sigma^2_Y = 2pq\,(c^2_1 + \cdots + c^2_s + c_1c_2 + \cdots + c_{s-1}c_s)$$
$$\sigma_{XY} = pq\,(b_1 + b_2)\,(c_1 + \cdots + c_s)$$

and thus the correlation between X and Y is

$$r_{XY} = \frac{(b_1 + b_2)(c_1 + \cdots + c_s)}{\sqrt{4(b^2_1 + b^2_2)(\Sigma c^2_j + \Sigma c_jc_{j'})}} \qquad j < j'$$

To maximize the value of r_{XY} we equate its derivatives with respect to the b's and c's to zero. Due to the symmetry of the expression for r_{XY}, the solution of these $2 + s$ equations is found to be that all the b's are equal and all the c's are equal, viz.,

$$b_i = b, \qquad c_j = c.$$

Thus, the maximum value of r_{XY} is

$$r_{XY} = \frac{2b \times sc}{\sqrt{4 \times 2b^2 \times \frac{1}{2}s(s+1)c^2}} = \sqrt{\frac{s}{s+1}}.$$

The correlation between one parent and s children may be obtained by setting either b_1 or b_2 equal to zero, yielding

$$r = \frac{b \times sc}{\sqrt{4b^2 \times \frac{1}{2}s(s+1)c^2}} = \sqrt{\frac{s}{2(s+1)}}.$$

This value coincides with the ordinary multiple correlation between a single variate x and a set of y's. Hence, the correlation listed in table 2 are the maximum values, obtained by giving equal weights to the father and mother and also equal weights to each of the children. The values of variances and covariances as given in table 2 are for the cases $b_i = c_j = 1$.

SUMMARY

With additive genic effects, the correlation coefficient between the sum (or average) of parental measurements and the sum (or average) of children's measurements is $\sqrt{s/(s+1)}$, where s is the size of the sibship. If only one parent of the sibship is known, the correlation is $\sqrt{s/2(s+1)}$. It has been shown that this correlation value is a maximum between the set of two parents and the set of s children.

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A Genetic Study of Progressive Spinal Muscular Atrophy

NTINOS C. MYRIANTHOPOULOS AND IAN A. BROWN

Dight Institute for Human Genetics, University of Minnesota, and Department of Neurology, University of Minnesota Hospitals

INTRODUCTION

PROGRESSIVE spinal muscular atrophy is a rare disease of the motor neurons within the central nervous system, the etiology of which is not entirely known. Very little information is available about the heredity of the disease because of the scanty occurrence of family histories in the literature, although all the available pedigrees indicate dominant transmission. The clinical aspects as well as the genetics of progressive spinal muscular atrophy, are further complicated by the fact that the syndrome is variable in its expression resulting in considerable confusion among workers in the field.

In this study two new pedigrees are reported, the chief importance of which lies in the presence of all three known variants of the syndrome in some of the members of the families. While this study is primarily concerned with the hereditary nature of the disease, it was thought that a short description, as well as a brief clinical discussion of the various manifestations of it, should be included, in the hope of bringing together the prevailing points of view on a matter which is not yet entirely settled. Such an endeavor should also contribute to a better understanding of the heredity of the disease.

A review of the existing genetic literature, along with selected pedigrees, is also presented, and while no claim can be made that it is exhaustive, it is hoped that it will give an adequate picture of the work done up to the present time.

DESCRIPTION OF THE DISEASE

It is generally agreed today that progressive spinal muscular atrophy is not a clear-cut pathological entity but can be expressed in a number of variants of a syndrome which is due to disease of the motor neurons within the central nervous system. There are no sharp lines of delimitation between the different expressions of the syndrome. The clinical manifestations of the syndrome are, wasting of the muscles of the upper and lower extremities, bulbar paralysis, and paralysis of the extrinsic muscles of the eyes.

Today, the generally accepted three types of progressive spinal muscular atrophy are as follows:

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1. Spinal form

a) *Aran-Duchenne type:* This is the most common type. Today it is not considered to be an independent entity, as originally imagined, but its relationship to amyotrophic lateral sclerosis and bulbar paralysis, although not yet completely resolved, is universally recognized.

In the majority of cases the muscles of the hands are first affected and the atrophy spreads slowly and progressively, extending to the arms and shoulder girdle. The muscles of the lower extremities become affected later in the course of the disease, but rarely does the disease start from the feet. The atrophy is often accompanied by fascicular twitching and disappearance of the deep reflexes.

Histopathologic changes are found essentially in the spinal cord, seldom in the medulla oblongata, cerebrum, or peripheral nerves. Occasionally they are found in the muscles themselves. Depending upon the stage of the disease, the anterior horn cells are found in various degrees of degeneration.

The disease usually starts after the third decade of life, is progressive and has a duration of a few to 30 years, ending in death.

b) *Amyotrophic lateral sclerosis (Charcot's disease):* This condition was first described by Charcot more than 75 years ago, who distinguished it from the Aran-Duchenne type of muscular atrophy on the grounds of degenerative changes found in the pyramidal tracts of the cord, and named it amyotrophic lateral sclerosis. Soon after, however, the validity of his distinction was questioned on clinical and histological grounds especially by German workers. Gowers (1903) considered their arguments and concluded that there was no valid distinction between the Charcot and Aran-Duchenne types.

The condition sets in late in life and usually the same atrophy and weakness is found as in the Aran-Duchenne type. In addition, there occurs a symmetrical sclerosis of the lateral tracts. As a result of this bilateral tract lesion, there is found a spastic paralysis in the legs with exaggeration of the deep reflexes and diminution or absence of the superficial ones.

Histopathologic changes essentially consist of destruction of the anterior horn cells and extreme demyelinization in the pyramidal tracts. Changes are frequently found in the Betz cells of the precentral gyrus. Thus, the characteristic changes are in the motor cortex and the corticospinal tracts. For this reason, Grinker (1945) thinks that progressive bulbar paralysis, progressive muscular atrophy and amyotrophic lateral sclerosis are all one and the same disease and need not be differentiated as diseases *sui generis*. Such a point of view is not entirely acceptable to all modern neurologists. Opinions range from consideration of progressive muscular atrophy as a form of amyotrophic lateral sclerosis (Best, 1931), to a mere component of it (Hassin and Dublin, 1945), to an entirely separate disease. Thus, Wechsler (1952), considers amyo-

trophic lateral sclerosis as a separate entity and does not include it in his classification of "progressive nuclear muscular atrophies."

2. Progressive bulbar paralysis

This name is given to a particular anatomical localization of the same degeneration process. The disease is today considered identical with progressive spinal muscular atrophy since persons with almost any of the spinal types develop bulbar paralysis if they live long enough. Persons affected with bulbar paralysis first, often develop the other expressions of the syndrome if they survive long enough to do so. Of the 83 cases collected by Collins, more than 25% began at the bulbar level, and so did 32% of Dana's 40 cases (quoted by Wilson, 1940).

The atrophic process usually involves the muscles supplied by the fifth, seventh, tenth and twelfth cranial nerves. The tongue begins to atrophy and exhibits fascicular twitching. The muscles for speaking, chewing and swallowing become affected and there is particular difficulty in guiding the bolus and in having it gripped by the pharyngeal constrictors. Liquids are often apt to go "the wrong way," and the patient often dies of bronchopneumonia as a result of aspiration of food or liquid particles.

3. Progressive external ophthalmoplegia (von Grafe's disease)

This is a slowly progressive affection characterized by paralysis of the extraocular muscles.

Ptosis of one or both eyelids is generally the first symptom, followed slowly by gradual spread to the external ocular muscles. Diplopia may occur.

The histopathology of the disease is not completely clear, mainly due to absence of necropsies on affected persons. Langdon and Cadwalader (1928), published what they believed to be the only case with necropsy. Their patient was a woman of 84, in whom the first symptoms were recognized at the age of 43 and were fully developed by the age of 75. Upon histological examination, the sixth nerve nuclei were recognized. The nerve cells appeared to have undergone slight chromatolysis, were diminished in number and varied in shape. The cells of the trochlear nuclei presented much the same picture. The authors pointed out the striking resemblance of the changes to those found in cases of progressive muscular atrophy of childhood, and thought that their case must be regarded as a similar form of chronic neuron degeneration, because it is the same pathological process that produces spinal muscular atrophy.

The condition appears usually during childhood or early youth, but it may also have late onset. It is never congenital, never fatal, but progressive in its course.

Although progressive external ophthalmoplegia is frequently found with one or all types of muscular atrophy, the chief objection to including it in the same

group rests on the fact that other spinal afflictions, like tabes dorsalis, are capable of producing it. Its existence as a separate entity is even more doubtful and not easily defendable. As Friendenwald (1922) put it, "in spite of the numerous cases published since von Grafe's first case in 1856, the existence of an isolated and independent form is more than doubtful. These cases are almost all complicated with progressiv muscular atrophy, amyotrophic lateral sclerosis, or tabes."

Wilbrand and Saenger, in their monumental work, *Die Neurologie des Auges* (1900), grouped progressive external ophthalmoplegia under nuclear paralyses, and defined it as unilateral or bilateral paralysis in which the abducens or the trochlear, or both nerves, are affected, in addition to the oculomotor, or several of its branches. They also presented 40 cases of ophthalmoplegia in combination with other types of muscular atrophy, as follows:

Ophthalmoplegia with bulbar paralysis: 20 cases

Ophthalmoplegia with spinal affection: 7 cases

Ophthalmoplegia with bulbar paralysis and spinal affection: 13 cases.

Marburg (quoted by Best, 1931), placed together progressive spinal muscular atrophy, progressive bulbar paralysis and progressive external ophthalmoplegia as one disease of the motor system, under the name "Amyotrophia muscularis progressiva." Wilson (1940) is more cautious for the reasons listed above. Although he lists progressive external ophthalmoplegia under the clinical types of progressive spinal muscular atrophy, he proceeds, "Whether this may come under the same category as the spinal and bulbar types is hard to decide, because more than one process is capable of producing it." He points out, however, that, "When other possibilities are excluded, a 'primary' class is left which might be regarded as one of 'pure' nuclear atrophy comparable to Duchenne's disease. There is no need to hesitate when this ophthalmoplegia precedes or follows bulbar palsy or its spinal analogues . . . ." Walsh (1947) is inclined to treat the condition as a separate entity on the grounds that it has infinitely better prognosis than the nuclear atrophies, and offers criteria for differential diagnosis. He recognizes, however, its association with the other types and reports a case of a woman with amyotrophic lateral sclerosis and bulbar affection, who at the last stages showed almost complete external ophthalmoplegia which spared only the inferior recti. Duke-Elder (1949) mentions only in passing, the relationship between external ophthalmoplegia and the muscular atrophies, while Wechsler (1952) includes chronic progressive ophthalmoplegia in his grouping of "progressive nuclear muscular atrophy."

REVIEW OF THE GENETIC LITERATURE

The etiology of the disease remains unclear despite much study and speculation. Recently, attempts have been made to study the disease in terms of biochemistry. This attempt has met with little success. Lovell (1932) was the

first to emphasize that a hereditary approach might provide a partial answer: "Notably lacking in the literature is the consideration of a familial predisposition as worthy explanation of the disease." Lovell's point is an important one. While heredity alone may not provide an adequate explanation, a study of the heredity of the disease in terms of physiology and biochemistry might give us the answer, as in the cases of phenylketonuria, alcaptonuria, tyrosinosis and many other metabolic diseases.

The disease is rare although well known. Its tendency to run in families was noticed by some early workers but most of them considered it to be non-hereditary. Aring and Cobb (1934) in their classification of the muscular atrophies and allied disorders, classified progressive muscular atrophy and amyotrophic lateral sclerosis as "sporadic" with no tendency to run in families, while McKinley (1939) referred to progressive muscular atrophy as usually not inherited. Grinker (1945) states that only occasionally can an hereditary or familial history be obtained, and Wilson (1940) observes that heredofamilial examples are far outnumbered by cases in which no hereditary factor can be found. There seems to be universal agreement that males are affected more frequently than females, by a ratio of 3 or 4 to 1.

Actually, hereditary cases are not as rare as they may seem to be. It is possible that new cases, with no family history, arise by mutation but one must also consider that the disease has a late onset. If potentially affected people die before they develop any symptoms, the disease may be manifested in an isolated case in a family and no hereditary influence ascribed to it. It is not improbable that the majority of the cases of progressive spinal muscular atrophy, are genetic. With the present knowledge of the disease it is doubtful whether a clinical differentiation can be made between cases of genetic and non-genetic origin.

A comprehensive review of the heredity of the disease is lacking in the literature. This may be accounted for, mainly by two reasons: firstly, by the rarity of the disease and hereditary cases of it; and secondly, by the inclination of earlier reviewers to treat neuromuscular and neurospinal cases as a unit, and to apply statistics to groups of diseases the components of which are genetically distinct. Such reviews (Kollaritis, 1906; Bremer, 1922; Boeters, 1938), while containing a wealth of material and excellent references, added to the already existing confusion. A quite detailed account of cases and literature is given by Gates (1946), but it shares the inaccuracies of others. It is hoped that the present review will help to clarify the situation somewhat.

One of the earliest hereditary cases on record is that of the Bessel family in Germany, published by Eichhorst (1873). The pedigree (fig. 1) presents the family history for six generations, involving 13 affected persons, eight males and five females. The clinical picture was one of typical, rapidly progressive muscular atrophy with bulbar involvement in the propositus, IV-8. The age

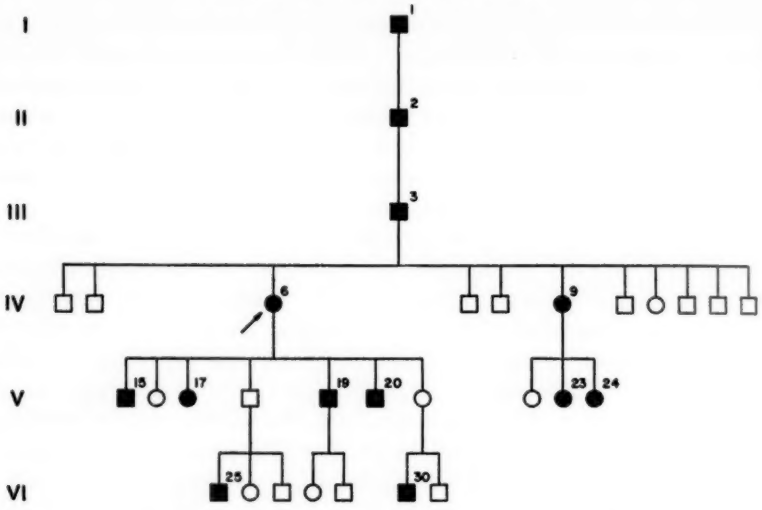

Fig. 1. Pedigree of the Bessel family (1873). After Eichhorst.

of onset ranged from eight to 26 years but only two cases were reported as starting at eight; the next youngest case started at 19 years. The inheritance is clearly a dominant one and although the sibs of the first three generations are not known, the trait seems to have complete penetrance.

This pedigree came to the attention of the famed Sir William Osler who published it along with a very interesting pedigree of his own (1880), that of the Farr family of Vermont (fig. 2). Dr. Osler's patient, III-9, complained of weakness in the left leg and peculiar twitching in the muscles of various parts of the body. The symptoms appeared at the age of 46 and the disease was progressive. The diagnosis was progressive muscular atrophy. His father, II-5, suffered from the same disease and died at 61 after being ill for two years. His aunt, II-7, died at 40 of paralysis, of unknown form. No age of onset is given

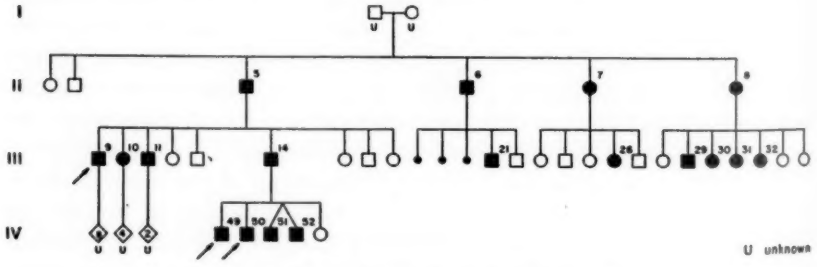

Fig. 2. Pedigree of the Farr Family of Vermont. After Osler (1880), and Brown (1951).

for the other sibs of generations II and III which are included in the original Osler pedigree. Of the 13 affected members in these two generations (excluding II-7), seven were males and six females.

Fortunately there was a follow-up study of the family by Dr. Madelaine Brown of Harvard University Medical School and Massachusetts General Hospital (1951), to whom we are indebted for extending the pedigree and for adding one of her own, which will be referred to later. Dr. Brown, digging into the records of the Massachusetts General Hospital, found that in 1905 a 35 year old man, member of the Farr family (IV-49), entered the Massachusetts General Hospital with progressive muscular atrophy. It was ascertained from him that his father, III-14, (affected at the age of 43), one of his affected uncles, and his grandfather II-5, developed bulbar paralysis and died of it. Dr. Brown was able to obtain several letters addressed to Dr. Osler, giving additional information about members of the family. Another patient, IV-50, who was under the care of Dr. Lane, proved to be a brother of the Massachusetts General Hospital patient. His symptoms started at the age of 36. Two other brothers of the same sibship who were twins, were also affected; one sister was not affected. The cause of death in the Vermont family, according to Dr. Brown's information, was bulbar paralysis. It was further ascertained that Dr. Osler's patient had eight children and that two of his affected sibs had four and two children respectively. Unfortunately nothing is known about them. Efforts are now being made to trace these members of the family. Since the inheritance is clearly dominant, approximately 50% of them should be affected.

Bernhardt (1889) published a pedigree of a German family with progressive muscular atrophy complicated with bulbar involvement (fig. 3). Of the five

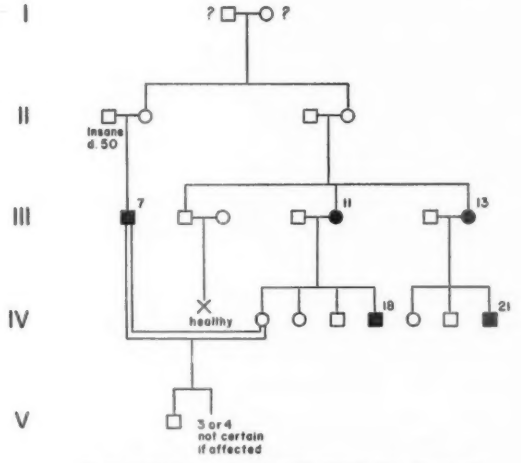

Fig 3. Pedigree of a German family (1889). After Bernhardt.

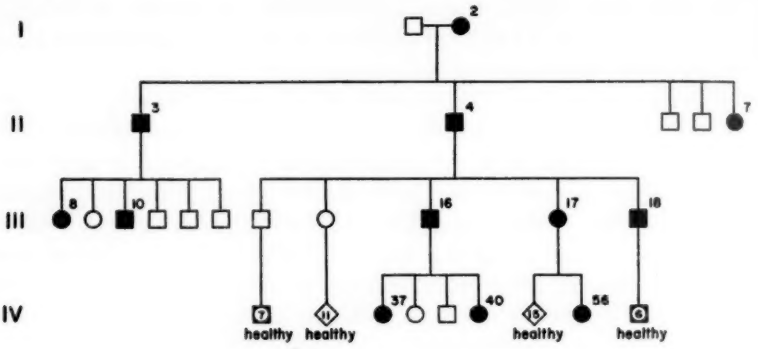

Fig. 4. Pedigree of a family with progressive external ophthalmoplegia (1900). After Beaumont.

affected members in two generations, three were males and two females. Three of them, III-7, IV-8 and IV-21, developed bulbar paralysis. There is a consanguineous marriage in the pedigree; III-7 married his first cousin once removed but there is no information as to whether any of their children were affected. The age of onset ranged from 32 to 50 years of age and the duration of the disease was about 2½ years. The heredity seems to be dominant.

Beaumont (1900) reported a family with progressive external ophthalmoplegia, in which 12 members were affected in four generations, five males and seven females (fig. 4). The affected members lived to a very old age and two are reported to have died at 85 and 90 years of age. The age of onset ranged from 22 to 40 years. The trait appears to be clearly dominant with complete penetrance.

Heard (1901) reported the case of a man age 50, with progressive external ophthalmoplegia. He had marked ptosis of the eyelids and complained of poor vision and inability to move either eye, alone or together. His two sons and a brother age 48 had drooping eyelids and could not move their eyeballs, and his father was practically blind with the same disease. Two sisters who died at an early age also had drooping eyelids and inability to move the eyeballs. No further information is given on the family, but the inheritance seems to be clearly dominant in this family too.

Kollaritis (1906) published numerous cases representing a variety of neuromuscular diseases under the general heading "Beiträge zur Kenntnis der vererbten Nervenkrankheiten." His, is a typical example of the prevailing point of view at the time, but considering the meager understanding of Genetics early in the 20th century, such an outlook should not seem surprising. He diagnosed one of his cases with family history as dystrophia musculorum progressiva; however, the symptoms and histologic examination which showed

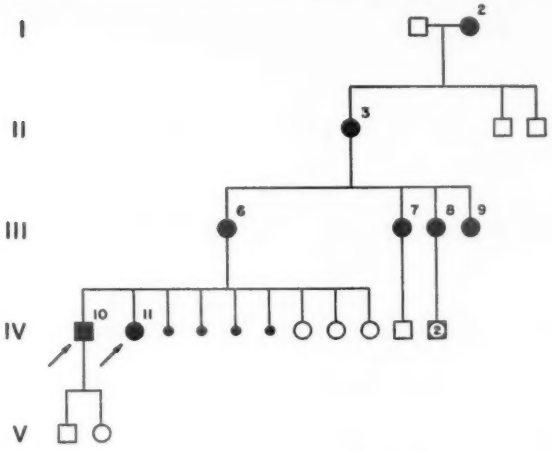

Fig. 5. Pedigree of a German family (1916). After Hoffmann.

degeneration of the lateral pyramidal cells of the spinal cord, suggest amyotrophic lateral sclerosis. Four members of the family were affected with identical symptoms.

Hoffmann (1916) reported the case of a German family with spinal affection (fig. 5), but he was at a loss to make a diagnosis. There were eight affected members, one male and seven females, in four generations. The propositus, IV-10, at the age of 28 developed difficulty in walking, articulation and swallowing; soon, he could not walk at all and his speech was not understandable. He had spastic paralysis and atrophy of the lower limbs, and also atrophy of the arm muscles which started from the small muscles of the hands. His sister, IV-11, at the age of 12 noticed difficulty in walking, articulation and swallowing, so that eating became a real problem for her. Later, she developed paralysis and atrophy of the arms, which also started with the small muscles of the hands. There was no atrophy in the leg muscles but her gait was spastic. The disease was progressive in both cases. Their mother had the same symptoms, and so did her three sisters, one of whom died of the disease at the age of 43. Their grandmother and great grandmother had the same symptoms.

Hoffmann considered the probability of multiple sclerosis and spastic paralysis but concluded that the clinical picture fitted better a "hereditary affection of the central nervous system." The disease was probably progressive spinal muscular atrophy with bulbar involvement. The heredity appears to be clearly dominant.

Bremer (1922) attempted a review of hereditary cases with pedigrees, and unfortunately, grouped his 13 cases under "Heredodegenerationen des Nerven-

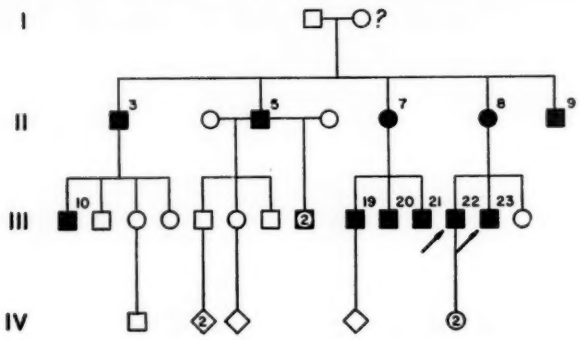

Fig. 6. Pedigree of the Montag family (1922). After Bremer.

systems." The relationship of his 13 cases to progressive spinal muscular atrophy is obscure and difficult to decide. Furthermore, no diagnosis was given for each case but the pedigrees were separated into seven with a dominant and six with a recessive mode of inheritance. No more details were given. Along with these cases Bremer published two selected pedigrees, with the members of one having symptoms "very similar to those of amyotrophic laterial sclerosis" (fig. 6). There were 11 affected persons in two generations, nine males and two females. The disease was highly progressive, and one member, III-23, seemingly had bulbar paralysis. The age of onset ranged from 20 to 50 years. Bremer observed that the disease affected males more severely and more frequently than females. Since the transmission was direct, he assumed a dominant, sex-linked gene which was suppressed in the female. Actually there is no reason why an assumption of sex-linkage should be made, because the ratio of *all* males to females (both affected and non-affected) in the family deviates greatly from the expected 1:1 ratio, in favor of the males. Furthermore, III-10 could not have received the gene from his father if complete sex-linkage were present.

Friedenwalt (1922) reported the case of a 19 year old girl who suddenly developed ptosis of the eyelids, at the age of 18, and also had diplopia when she looked up. Of her eight sibs, her older brother had congenital ptosis of the right eye. Her condition was slowly progressive. No further details about the family were given.

Fürst (1929) and Steinthal (1929) reported a case each of progressive muscular atrophy in which the transmission seemed to be an autosomal recessive. In Fürst's family there were three affected members, all males, in two generations, with age of onset about the first year after birth. In Steinthal's family (fig. 7) there were five affected members, two males and three females, in two

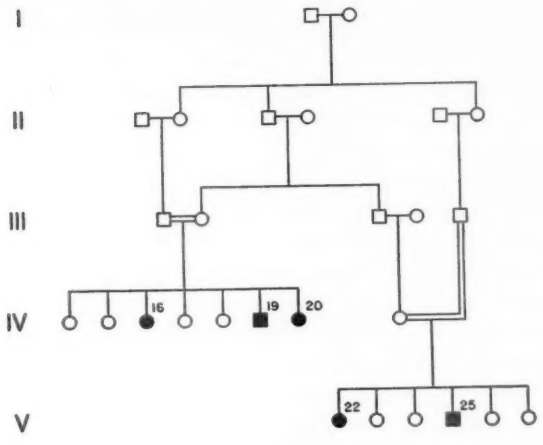

Fig. 7. Steinthal's pedigree (1929).

generations, with the age of onset ranging from one to six years of age. In this family there were two consanguineous marriages: one first cousin marriage, and the other of first cousins once removed. Steinthal describes the disease as a typical picture of progressive muscular atrophy. Both cases, however, judged by the age of onset, are probably good examples of infantile muscular atrophy (Werdnig-Hoffmann type) which is mostly transmitted as a recessive. They are included here only to demonstrate the difficulty involved in making the correct diagnosis of such neurological diseases. They also show how the knowledge of the heredity of such diseases may help in correctly diagnosing them, the recessive heredity distinguishing these two cases from dominant adult muscular atrophy.

Lovell (1932) reported the case of a woman 66 years of age, with progressive bulbar paralysis. Upon admission to the University of Michigan Hospital she complained of difficulty in speaking which started a few months earlier. Very shortly the disease progressed so that she had great difficulty in swallowing. The patient's mother had a similar condition and died at the age of 65, following a year's illness. Her mother's brother also died at about the same age with the same disease, and his son likewise died of it in the fifth decade of life. Lovell reaches the somewhat fantastic conclusion that "the disease appears to be transmitted as a recessive, non sex-linked mendelian trait." Gates (1946), who refers to this pedigree, considers it as an irregular dominant, but there is no reason why irregularity of expression should be assumed, since the disease has a late onset and no information is available about the patient's grandparents.

Moleen, Johnson and Dixon (1932) reported the case of three brothers with

progressive muscular atrophy and bulbar paralysis, one of whom was followed for 21 years. Their mother was in good health and their father died of pneumonia (age at death not given). They had three brothers and one sister, all in good health. The symptoms, pronounced weakness and wasting in the hands and arms, were present and identical in all three brothers. One died of myocarditis and auricular fibrillation and the propositus died of complete exhaustion. The third was alive at the time the case was reported. The propositus noticed at the age of 39 slight difficulty in articulation and in moving the tongue. Soon thereafter he noticed weakness in the hands and arms, and four years later weakness in the leg muscles became evident. The patient died 29 years after the onset of the first symptoms, of complete exhaustion. Upon microscopic examination it was found that the anterior horn cells in the first and fourth lumbar segments were diminished by 30% and that there was much evidence of shrinkage.

Sanders (1934) reported the case of a family with periodic paralysis and muscular atrophy. There were 14 affected members, ten with periodic paralysis and four with both periodic paralysis and muscular atrophy, in three generations (fig. 8). Of the latter, three were males and one female. Although actual ages of onset for the muscular atrophy were not given, it was stated that the symptoms appeared during the last five to ten years of the affected individuals' lives. Sanders postulated two hereditary factors, both dominant, and separate for each disease.

Brown (1951), published, along with Osler's pedigree, the pedigree of a Massachusetts family with progressive spinal muscular atrophy (fig. 9). In this family there were eight affected persons, six males and two females, in four generations. The propositus, IV-21, at the age of 40 was admitted to the Massachusetts General Hospital with progressive muscular atrophy which was well known among his ancestors and neighbors as "The Wetherbee Ail."

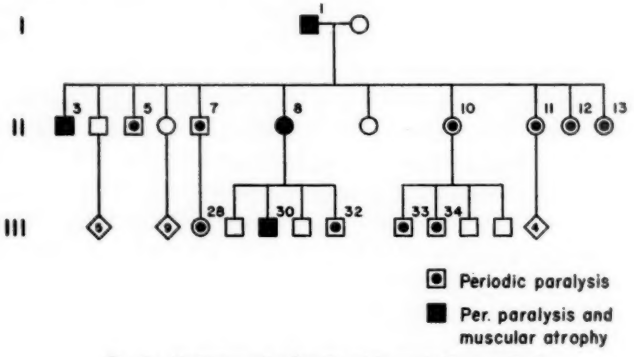

Fig. 8. Pedigree of a family with periodic paralysis and muscular atrophy (1934). After Sanders.

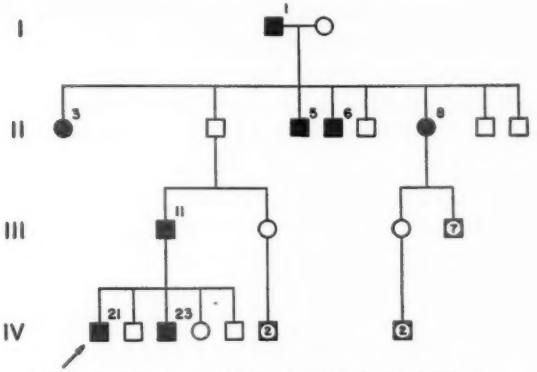

Fig. 9. Pedigree of a Massachusetts family (1872). After Brown (1951).

His great grandfather had progressive muscular atrophy and died of it; his grandfather was not affected but there is information that he died young. His father at the age of 39 had a slight limp in his walk, and weakness in his right thumb. The progress of the disease was rapid, affecting the muscles of the arms and legs, which diminished in size. He died a little over two years after the onset of the first symptoms. A brother of the patient was also affected and had the same symptoms, tremulous twitching, severe cramps and difficulty in walking. The inheritance is clearly dominant.

Robertson (1953) reported the case of a family with bulbar paralysis (fig. 10). Actually, it becomes evident from the history that bulbar paralysis was only a differential expression of progressive spinal muscular atrophy. There

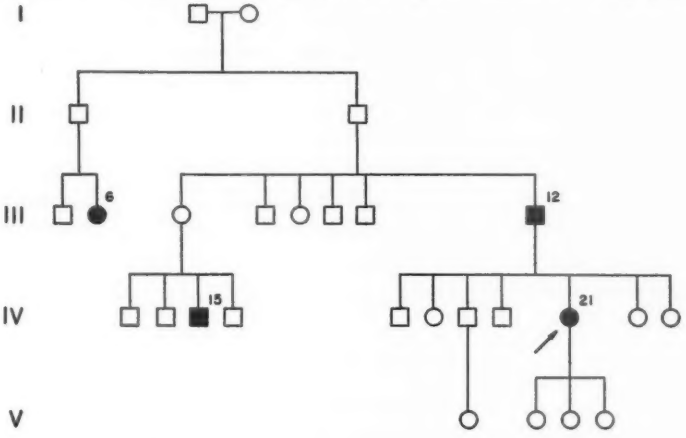

Fig. 10. Robertson's pedigree (1953).

were four affected persons, two males and two females, in two generations. The propositus, IV-21, noticed at the age of 65 defect in articulation which progressed, and by the age of 69 she had great difficulty in swallowing. In the paper, great importance is placed on the patient's mental condition which showed gradual decline of mental capacities and presence of delusions. Physically, no muscular wasting was found. The patient died in 1950.

The patient's father died of progressive muscular atrophy at the age of 69. His symptoms started with difficulty in articulation and swallowing and subsequent weakness and loss of power in all four limbs. A cousin of the father died of paralysis of the throat at the age of 60 and a nephew of the father died of bulbar paralysis at the age of 64. Robertson concludes that the genetic basis is an autosomal dominant showing irregularity in its expression.

SOURCES OF DATA

The two propositi of the pedigrees presented in this study were patients at the University of Minnesota Hospitals. The data have been collected from the records of the University of Minnesota Hospitals, the Mayo Clinic, Saint Joseph Hospital at Saint Paul, Minnesota, Saint Peter State Hospital at Saint Peter, Minnesota, private physicians, and also by interviews with the patients and their immediate relatives. The members of the first affected generations in both families were immigrants to the United States; in the case of family K, from Czechoslovakia, and in the case of family P, from Canada.

In about half the affected members of these families, more than one or all three variants of the syndrome were found. Three separate symbols have been employed to designate the variants of the syndrome, namely the spinal form, progressive bulbar paralysis and progressive external ophthalmoplegia, but this distinction must not be taken to mean that the variants are considered as separate entities. It was done only to help detect genetic segregation if such existed, which apparently is not the case.

The fourth and fifth generations in both families have been recorded in the pedigrees although no member of them is affected as yet. The members of the fourth generation are now in their forties or fifties, and those of the fifth generation, in their twenties or thirties. Since the age of onset in both families is very late, it is too early to know whether any one of them may become affected. Their records and particulars are kept in the files of the Dight Institute for Human Genetics of the University of Minnesota, with a view to a follow-up study.

DESCRIPTION OF THE PEDIGREES

Family K. (fig. 11)

This family has two main branches, the parents of which II-10 × 13 and II-11 × 12, came to the United States from Bohemia. There are ten affected

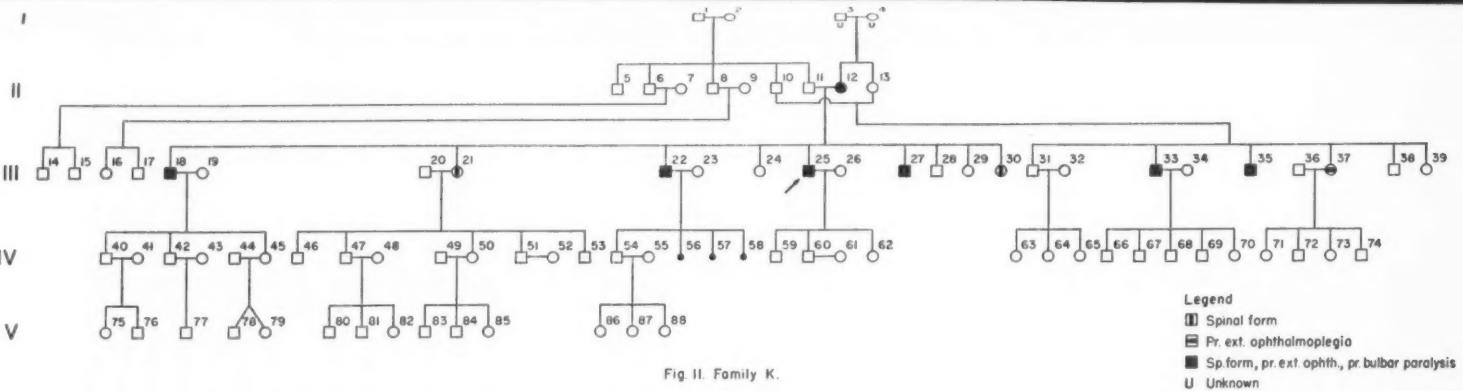

Fig. 11. Family K.

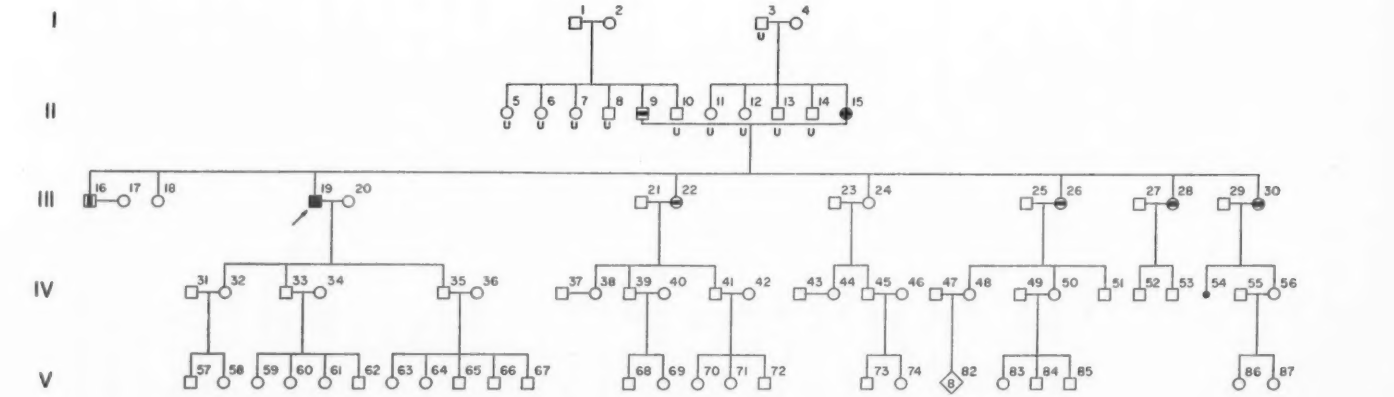

Fig. 12. Family P.

Legend as for family K

members in two generations, six males and four females. The six male members have all three manifestations of the syndrome, while only one female has all three of them.

In the second generation, there is one affected female, II-12. Her spouse, II-11, was not affected. Her sister, II-13, married II-12's husband's brother, that is two sisters married two brothers. Neither II-10 or II-13 were affected, but II-13 is known to have died at the age of 56. Nothing is known of the womens' parents except that their mother died at the age of 91. The family of their husbands appears to have been free of the trait. A member of the family serving with the United States Armed Forces during world war II, visited Bohemia and was able to trace the paternal side of the family, as shown in the pedigree. None of them was affected.

II-12: Female; born 11-1-1853 in Pohorence, Bohemia; died 11-19-1934 in Beroun, Minnesota, of bronchopneumonia. She had difficulty in swallowing for a long time before her death and at the age of 60 she developed drooping eyelids. At the age of 73 she noticed weakness in her legs, which rapidly progressed, and for a few years prior to her death she was unable to walk. Her bulbar condition and drooping of the eyelids also became progressively worse, and during her later years she could not open her eyes. She married II-11, who was born on 4-10-1846, in Kloub, Bohemia, and died on 11-25-1926. As far as it is known, he was not affected. They had nine children, one of whom, III-24, died in infancy. Six of their children were affected, four males and two females.

II-13: Female, sister of II-12. Not very much is known about her except that she died at the age of 56, and the cause of her death has not been ascertained. Our informant, her son III-35, noted that his affliction must have been handed down to him by his mother, but since the symptoms usually appeared at about the age of 60, she did not live long enough to develop them. Such an excellent understanding of human genetics by the laity is indeed surprising but also encouraging. She married her sister's husband's brother. They had six children, three of whom are affected, two males and one female.

III-18: Male, son of II-12; born 11-14-1875 in Albrechtice, Bohemia; died 4-46-1952 in Wahpeton, North Dakota, of progressive muscular atrophy. He had weakness in his leg muscles characterized by inability to raise his legs. He also had difficulty in swallowing, and drooping eyelids. The symptoms first appeared at the age of 55 and gradually progressed, resulting in his death. He was married and had three children, none of whom is affected as yet.

III-21: Female, daughter of II-12; born 12-20-1879 in Albrechtice, Bohemia; died 7-24-1938 in Beroun, Minnesota of pernicious anemia. For 20 years prior to her death she was suffering from marked anemia, menorrhagea and fibrosis of the uterus. She was also institutionalized for a short period of time for a mental condition due to nervous breakdown. At the age of 45 she noticed

weakness in her legs and had difficulty in walking which became worse, and by the time of her death she was almost completely paralyzed. Upon examination a positive Babinski was obtained but coordination of arms and legs was very poor. She also had flat feet. She was married and had five children, none of whom is affected as yet. From the available clinical information, this patient cannot be considered as more than a questionable case of progressive spinal muscular atrophy.

III-22: Male, son of II-12; born 6-10-1880 in Albrechtice, Bohemia; died 11-12-1945 in Britton, South Dakota of coronary thrombosis. At the age of 50 the first symptoms of external ophthalmoplegia appeared, and the ptosis was progressive. He was operated upon for bilateral ptosis in 1942 and according to the surgeon's report, who examined him one year after the operation, the results were excellent. At the age of 60 he noticed difficulty in swallowing, especially cold water, and also weakness in the leg and back muscles, which had a very progressive course. This extreme muscle weakness never affected his arms or hands. He entered the Mayo clinic, and upon examination he was found to have a grade 3 spondylolisthesis, hypertrophic changes in the left knee, and a pelvic facial-type of muscular dystrophy. Examination of the nose and throat was essentially negative, except that a definite weakness of the pharyngeal constrictors was noticed. The diagnoses acknowledge two variants of progressive spinal muscular atrophy, namely, progressive external ophthalmoplegia and bulbar paralysis, plus muscular dystrophy, as indicated by the hypertrophic changes. The diagnostic aspect of the disease, of course, is left entirely to the clinician. However, this case would seem to be one of muscular atrophy, and not dystrophy, when one considers all factors concerned, particularly the family history. The patient was married and had one son, now living and well. There were three miscarriages after the son's birth.

III-25: The propositus; male, son of II-12; born 9-5-1885 in New Prague, Minnesota; died 1-13-1953 at the University of Minnesota Hospitals of progressive muscular atrophy and bilateral bronchopneumonia. At about the age of 60 he noticed definite weakness in his legs, difficulty in swallowing and drooping of his eyelids. The weakness became progressively generalized and more marked in the legs. He entered the University of Minnesota Hospitals on January 11, 1953, and upon examination he was found very weak and in respiratory distress; he was unable to speak. His limbs were flaccid and the reflexes hyperactive. He had bilateral paralysis of the extrinsic muscles of the eyes with some limitation of upward gaze and lateral movement; he also had diplopia. The wasting of muscles was generalized but there were no fasciculations. There was a -2 weakness of the facial muscles, the tongue and jaw muscles, as well as the muscles of all extremities. The diagnosis was progressive spinal muscular atrophy. The patient died within two days after admission to the hospital. An autopsy was performed. The brain showed no gross pathology.

The spinal cord was essentially normal in appearance, except that it was slightly smaller than usual, and there appeared to be a finely diffused light brown pigmentation about the upper portion of the cord.

Microscopic examination of sections of psoas, diaphragm and intercostal muscles showed that they were essentially normal. Sections through multiple areas of the cerebral cortex and the white matter showed mild regressive changes in the cortical neurons, with many containing lipoid pigment. There was observed mild perivascular demyelinization. A section through the midbrain showed no pathological alterations of the third nerve. Section through the medulla oblongata was negative. Sections of the spinal cord showed changes compatible with the age of the patient. There was a striking decrease of the number of the anterior horn cells in some sections, especially in the cervical and lumbar segments, with shrinkage and hyperchromaticity of many of the residual cells. The most important changes observed were: Demyelinization, which was acute and recent; and alterations in the anterior horn cells, which appeared to have been of long duration. On the basis of the above, the diagnosis of progressive spinal muscular atrophy and arteriosclerosis was made. The patient was married and had three children, none of whom is now affected.

III-27: Male, son of II-12; born 10-13-1887 in New Prague, Minnesota; still living. At the age of 60 he felt weakness in the leg muscles and also difficulty in swallowing. At about the same time he noticed drooping of his eyelids. The symptoms became progressively worse and now he has considerable difficulty in walking. He is not married.

III-30: Female, daughter of II-12; born 6-16-1895 in Loyalton, South Dakota; still living. A few years ago she noticed some slight weakness in her legs. Although she now has considerable difficulty in walking, she states that she enjoys working in her garden. She is not married.

III-33: Male, son of II-13; born in November 1883 in Ipswich, South Dakota; still living. At the age of 56 he noticed symptoms of weakness in his leg and arm muscles, difficulty in swallowing and drooping eyelids. The weakness became progressively worse and the patient went through the Mayo Clinic, where his condition was diagnosed as progressive muscular atrophy. No details of his case could be obtained because the patient declined to give any further information or permission for examination of his record. He is married and has five children, all living and in good health.

III-35: Male, son of II-13; born in May 1888 in Ipswich, South Dakota; still living. At the age of 54 he began having some difficulty in swallowing and four years later he had a definite drooping of his eyelids. At about the same time he noticed some slight weakness in his arms. He went through the Mayo Clinic in 1949 and again in 1951. His examination showed a definite bilateral ptosis which did not respond to the use of prostigmin. The deep reflexes were present but slightly diminished. There was a definite weakness of

the muscles of deglutition. The neck muscles, shoulder girdle muscles and extending into the upper extremities showed some slight weakness. The diagnosis of progressive muscular atrophy was made, "in the absence of any other definite diagnostic findings." The patient is not married.

III-37: Female, daughter of II-13; born in September 1897 in Ipswich, South Dakota; still living. At the age of 53 she started having some difficulty in swallowing, and at the age of 57 her eyelids began drooping. Recently she has complained that her condition is getting progressively worse, and that her eyelids feel very heavy, especially in humid weather. She is married and has four children, none of whom is affected.

Family P. (Fig. 12)

The members of this family are very well aware that the disease is hereditary, and are very eager to point out that drooping eyelids "runs in the family." There are eight affected members in two generations, three males and five females. Four females, however, have only external ophthalmoplegia. The parents, II-9 and II-15, were both affected, but unfortunately not enought information is available about them. There is no consanguineous marriage in the family.

II-9: Male; born in 1831 in Canada; died in 1920 of bronchitis. At about the age of 50 he developed drooping eyelids, which became progressively worse with age. He had no other symptoms of muscular atrophy. He married II-15 and had eight children, six of whom became affected in their later years. Nothing is known about his parents, except that they both died young.

II-15: Female, wife of II-9; born in 1842 in Canada; died in 1905 of heart ailment. At about the age of 50 she also developed drooping eyelids, and about one year before she died she felt very weak in the legs and was unable to walk unassisted. Nothing is known about her parents, except that her mother died young.

III-16: Male, son of II-15; born in 1886; died in 1934 of a variety of diseases. At the age of 60 he felt weakness in his legs and difficulty in walking. In 1927 he was admitted to the Mayo Clinic, and upon examination he was found to have numbness and twitching in all four extremities, unsteady gait and loss of deep reflexes. The Babinski sign was present on the left. The diagnosis of combined sclerosis was made. Combined sclerosis is a disease characterized by sclerosis of the lateral, as well as the dorsal parts of the spinal cord. It is considered to be a disease *sui generis* usually associated with pernicious anemia. The patient returned to the Mayo Clinic for recheck of his condition, and in 1933 additional diagnoses of erythromelalgia bilateral recurrent inguinal hernias, prostatic hypertrophy, and left spermacoele, were made. The patient died eight years after the onset of the first symptoms. He was married but had no children.

III-19: The propositus; male, son of II-15; born 9-1-1869 in Canada; still living. At the age of 50 he noticed the first symptoms of ptosis, and since then the drooping became much worse, so that today he has to hold his eyelids up with clamps in order to be able to see. At the age of 60 he felt pains in the hip and weakness in his legs, which today keeps him confined to the wheel chair. At the age of 69 he felt slight difficulty in swallowing, which has also had a progressive course. In January 1953 he entered the University of Minnesota Hospitals with suspected carcinoma of the prostate, but upon operation it was found to be benign hypertrophy.

Physical examination showed equal and bilateral ptosis of the eyelids with limited movement of the eyebrows. There was a slight weakness of the tongue and all the facial muscles but no atrophy. Generalized paresis of all the trunk and limb muscles without fibrillation was observed, and also muscular atrophy which was most pronounced in the lower extremities. There was a -1 to -2 weakness in the muscles of the upper extremities, and a -2 to -3 weakness in the muscles of the lower extremities. Deep tendon reflexes were completely absent. The patient also suffered from severe arteriosclerosis and arthritis. The diagnosis was progressive myelopathic muscular atrophy. The patient is married and has three children, none of whom is affected.

III-22: Female, daughter of II-15; born in 1872; died in an accident in 1939. At the age of 40 she had drooping eyelids which became progressively worse and she had the condition surgically corrected. She was married and had three children, none of whom is affected as yet.

III-26: Female, daughter of II-15; born in 1877; still living. At the age of 50 she had drooping eyelids. She is married and has three children, none of whom is affected as yet.

III-28: Female, daughter of II-15; born in 1880; still living. At the age of 50 she had drooping eyelids which even today is of very mild form. For the past eight years she has had some difficulty in swallowing, which recently became worse. For some years she has been suffering from rather severe arthritis, following an accident. She is a widow and has one living son who is not affected. Another son died in childhood.

III-30: Female, daughter of II-15; born in 1882; still living. At the age of 50 she had drooping eyelids with a slightly progressive course. She is married and has one daughter who is not affected.

DISCUSSION

In the two new pedigrees presented in this study there are 18 affected individuals, nine males and nine females, in two generations. This is a perfect sex ratio. However, there seems to be agreement in the literature that there exists an excess of affected males over females of about 3 or 4 to 1. A count of the affected members of the cases reviewed in this study yielded 61 males

TABLE 1.—SEX RATIO OF AFFECTED TO NON-AFFECTED MEMBERS OF THE REVIEWED PEDIGREES

Sibships	Affected			Non-Affected		
	Males	Females	Total	Males	Females	Total
23	37	28	65	39	28	67

to 42 females. Among 23 sibships who had one affected parent there were 37 affected males to 28 affected females. The difference is indeed suggestive of a significant excess of males but about the same difference was found among the non-affected members of these sibships, 39 males to 28 females (see table 1). When one considers the proportion of total males to total females, the difference is not statistically significant. It is not possible to say with certainty at the present time whether the trait is fully penetrant in both sexes because of the limited sample and the great span of time over which it was collected. It might well be that the male, who in most cases is the bread-winner, is much more impaired in his work by the disease than the female, and his case comes to the attention of the investigator more often.

A far more subtle and intricate problem is that of the expressivity of the trait. In both families the transmission is direct, and it is not difficult to postulate dominant inheritance with complete penetrance. This is in full accord with the findings of the cases reviewed in this study all of which (excepting the disputed cases of Fürst and Steinthal) showed dominant inheritance. Such a postulate, of course, requires one underlying assumption: that the three expressions of the disease are not separate entities, but variants of one syndrome, progressive spinal muscular atrophy. That this is the case, is quite evident. In family K, the affected parent had all three variants, while in family P one parent had external ophthalmoplegia, and the other, external ophthalmoplegia and probably muscular atrophy of the legs. In both families, the affected offspring exhibited one, two, or all three variants, which should not be the case in either family if the variants were independent diseases. Considering the rarity of the disease, it is reasonable to assume that the affected parent of family K was heterozygous.

It is also reasonable to assume that both affected parents of family P were heterozygous. Neither of the affected parents in family P had bulbar paralysis, but some of their children developed it. One of the parents had muscular atrophy of the lower extremities, but only one, or possibly two, of their children developed it.

The level at which the various symptoms appeared did not follow a definite pattern in either family but varied randomly. Of the ten cases that had more than one variant of the syndrome, three started with external ophthalmoplegia, and in the remaining four all three symptoms appeared almost simultaneously. It is justifiable, therefore, to postulate that the disease is a genetic entity which

may be expressed as three variants, and that a single dominant gene with differential expressivity is responsible for the transmission of the disease. If such is the case, it is evident that the trait has lower expressivity in the female than in the male. Of the nine males affected in both families, seven had all three variants, while of the nine females affected only one had all three.

The question of age of onset is exceedingly important from both the eugenic and social points of view, as illustrated by other hereditary diseases of late onset, such as Huntington's chorea. The age of onset of the disease in both families ranged from 40 to 60 years with an average of 52 years. These figures are a little higher than those found in the reviewed cases, but the difference may be attributed to family constitutional variation. One point must be made at this time. It was stated earlier that the second branch of family K were descendants of II-10 and II-13, neither of whom was affected. It has also been ascertained that the family of II-10 did not have the trait and that he was free of it. On the other hand, II-13 had an affected sister, and she herself died at the age of 56. It is reasonable to assume, since she had affected children, that she carried the gene but did not develop the disease because she died before it was manifested, as her son pointed out. This is an excellent example of the many perplexing complications found in hereditary diseases with late onset.

It was pointed out earlier that no consanguineous marriage was known in family P, in which both parents were affected. Considering the rarity of the gene, it would not be improbable that the two affected parents, both of French-Canadian stock, were actually distant relatives, descendants of the same family in which the disease originated. Such a hypothesis, of course, is purely speculative.

Since there is good reason to believe that both parents in family P were heterozygous, one fourth of their offspring would normally be expected to be homozygous dominant. It would certainly be of great interest if they could be distinguished from the heterozygotes. Unfortunately, the present-day knowledge of the symptomatology and histopathology of the disease does not permit the differentiation between the heterozygote and the homozygous dominant. An attempt to do so on the basis of the severity of disease among the sibs of this family proved unsuccessful.

In order to decide whether any bias was involved in the collecting and recording of the reviewed pedigrees, in favor of affected members, a count was taken of the affected to nonaffected sibs who had one affected parent. The members of the last affected generation were excluded in order to avoid statistical artefacts resulting from the late onset of the disease. Practically, there should be about equal numbers of affected and non-affected sibs. The results are presented in table I. The totals, 65 affected to 67 non-affected, indicate that the pedigrees are a relatively unbiased selection.

It has not been possible at the present time to calculate a mutation rate for the dominant gene responsible for progressive spinal muscular atrophy because of lack of sufficient data.

SUMMARY

1. Progressive spinal muscular atrophy is a rare disease of the motor neurons within the central nervous system which may be expressed as atrophy of the muscles of the extremities (Aran-Duchenne type, Charcot's disease), as progressive bulbar paralysis and as progressive external ophthalmoplegia. There is some disagreement in the literature as to whether the disease should be considered from such a broad point of view.

2. Progressive spinal muscular atrophy has been considered by various authors to be sporadic and very rarely hereditary, although several cases with family history are found in the literature. There appears to be a definite genetic variety of this disease.

3. A survey of the existing genetic literature has been made and in all cases a dominant mode of transmission has been found. The disease seems to affect males more severely than females. All the complete pedigrees which could be found in the literature have been reproduced in this study.

4. Two new pedigrees of families with progressive spinal muscular atrophy have been presented. From a genetic study of these pedigrees it appears that the disease is a genetic entity capable of being expressed on one or more variants of the syndrome, and that a single dominant gene with differential expressivity is responsible for its transmission.

5. It has not been possible to calculate a mutation rate for this gene because of lack of adequate data.

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A Method of Estimating the Frequency of Abnormal Autosomal Recessive Genes in Man

HERMAN M. SLATIS

Department of Genetics, McGill University, Montreal 2, Canada

WITHIN the past few years it has become obvious that the average person must be carrying a number of genes for abnormalities, but not even the order of magnitude of this number has been estimated from any observations. Muller (1950), by making various assumptions, has estimated on the basis of indirect information that there is a minimum of approximately eight deleterious genes per person. Recently Reed (1954) has noted that reasonably unbiased information on recessive genes may be obtained from the rare father-daughter and brother-sister matings which occur in man.

Because father-daughter and brother-sister matings are rare, they would yield information at a very slow rate. However, if the average number of recessives is large, even first cousin marriages should produce offspring indicating the inheritance of a number of genes in common. Since information on moderately large numbers of first cousin marriages can be collected, this would afford an excellent mode of calculating the probable number of abnormal recessive genes in man directly from observational data.

METHODS

When dealing statistically with mutants among the progeny of related individuals it is necessary to assume that almost all of the autosomal recessive characters that occur are due to inheritance from the common ancestors, rather than chance inheritance from separate sources or inheritance plus mutation. It is known that rare recessives are characterised by an elevated frequency among the progeny of related individuals. Therefore, it is reasonable to make the converse assumption, namely that almost all rare recessives in the progeny of close relatives are due to inheritance from a common ancestor.

If an individual is heterozygous for a given abnormal recessive gene, the likelihood that a given descendant will also carry the gene is $\frac{1}{2}^x$, where x is the number of generations between the individual and the descendant. Thus, a child will have the gene in one half the cases and a grandchild will have it in one quarter of the cases. Since the chance that two relatives will carry the same gene is the product of the chance that each will have it, a brother and sister will both be heterozygous for a quarter of the abnormal genes which

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TABLE 1. CONSTANTS CONCERNED WITH THE RELATIONSHIP BETWEEN FAMILY SIZE AND THE EXPRESSION OF A RECESSIVE GENE

s	$\frac{3}{4}^s$	z	$\frac{1}{z}$
1	.75	.25	4.0
2	.5625	.4375	2.286
3	.4219	.5781	1.730
4	.3164	.6836	1.463
5	.2373	.7627	1.311
6	.1780	.8220	1.217
7	.1335	.8665	1.154
8	.1001	.8999	1.111
9	.0751	.9249	1.081
10	.0563	.9437	1.060

s = sibship size.
$z = 1 - \frac{3}{4}^s$.

either of their parents carried in the heterozygous state, a pair of first cousins will both be heterozygous for one sixteenth of the genes carried by their common grandparents, and a pair of second cousins would both have only one sixty-fourth of the genes which their common great-grandparents carried.

There is, of course, the possibility that two persons will be heterozygous for the same recessive character without manifesting it among their progeny. The likelihood that such a recessive character will not be manifested is $\frac{3}{4}^s$, where s is the number of children which the couple has had. The value of this figure is given in table 1, and it will be seen that failure to manifest a recessive character decreases rapidly as family size increases. Also shown in table 1 is the value $1 - \frac{3}{4}^s$, which has been called z. This statistic may be interpreted as the probability that at least one of their progeny will show a recessive gene that is heterozygous in both parents of a family of size s. Table 1 also contains the reciprocal of z.

Assuming that the effects of two or more abnormal genes can be observed independently, the distribution of homozygous recessives among the s progeny of a cross will be observed to be random. It must also be assumed that the average number of abnormal genes will be the same among the parents of families of various sizes (it is readily admitted that there are many factors such as fear of having another affected child or overcompensation to replace lost children which could be postulated to give a positive or a negative correlation between family size and the number of abnormal genes, but the cumulative effect is probably not too far from zero). Even though the average number of abnormal genes possessed by both of the parents of a sibship is assumed to be the same for sibships of all sizes, the proportion of these genes which is expressed, z, is a function of the family size. If $\bar{r}$, the average number of reces-

sive genes observed to be segregating in families of size s, is multiplied by $\frac{1}{z}$, one obtains $\bar{c}$, the average number of abnormal genes calculated to be carried in common by the parents of the sibships. For example, the number of observed abnormal genes among families with one child is one fourth of the probable number of such conditions that the parents of these families carried. Therefore, the observed value must be multiplied by 4.0 to get the calculated total number of recessives carried.

An overall estimate of $\bar{c}$, called $\bar{\bar{c}}$, can be derived by dividing the number of mutants observed among the ascertained families, Σr, by a value expressive of the observable proportion of the recessives carried in common by both parents. If n is the number of families observed of each size and z is the proportion of recessives which will be expressed, Σzn is an appropriate measure of the frequency with which recessives would have been observed. Therefore, $\bar{\bar{c}}$ is equal to $\frac{\Sigma r}{\Sigma zn}$.

An alternative method of deriving $\bar{\bar{c}}$ is based on the fact that r is distributed in a Poisson manner. Therefore, the variance of $\bar{r}$ based on n sibships is $\frac{\bar{r}}{n}$. Since $\bar{c}$ is equal to $\frac{\bar{r}}{z}$, the standard deviation of $\bar{c}$ is equal to the standard deviation of $\bar{r}$ divided by z and the variance of $\bar{c}$ is equal to the variance of $\bar{r}$ divided by z^2, or $\frac{\bar{r}}{nz^2}$. Since all of the observed values of $\bar{r}$ are merely estimates of the appropriate value of z times $\bar{c}$, $\bar{c}z$ substituted for $\bar{r}$ gives $\frac{\bar{\bar{c}}z}{nz^2}$, or $\frac{\bar{\bar{c}}}{nz}$, as the variance of $\bar{c}$. To derive $\bar{\bar{c}}$, each value of $\bar{c}$ should be weighted by the reciprocal of its own variance and summed, and this sum should be divided by the sum of the weights. As the constant value $\bar{\bar{c}}$ appears in the denominator of each term, it may be dropped, making the formula for the estimate of $\bar{\bar{c}}$ equal to $\frac{\Sigma \bar{c}nz}{\Sigma nz}$, where summation is carried out over all observed sibship sizes. As $\bar{c}nz$ is equal to r, this formula may be written as $\frac{\Sigma r}{\Sigma nz}$, which is identical with the formula given above.

The standard error of $\bar{\bar{c}}$ is $\sqrt{\frac{\bar{\bar{c}}}{\Sigma nz}}$. However, the distribution of $\bar{\bar{c}}$ is skewed in such a manner that the probability that $\bar{\bar{c}}$ really lies a given distance above the calculated value will be greater than the probability that it lies the same distance below the calculated value.

APPLICATION TO DATA

Figure 1 is a list of 17 families in which the parents are first cousins. The families are arranged according to the number of live born children. Three miscarriages have been omitted. The single case of identical twins is considered as one child. Defects which are presumed to be due to simple recessive genes are indicated, and the defect is identified. These family data were collected largely because of the routine follow-up of an entry on a hospital questionnaire which asks for information on the consanguinity of the parents of children seeking treatment. Because of this method of ascertainment, the only major bias among families with live born children is that the propositi may be detected because of the occurrence of the defects which are being investigated. It will be seen that this occurred in four of the nine defects which have been found. There is a further bias because the consanguinity in the case of Morquio's disease was discovered when the family history was taken because of the nature of the disease, and the cases of deaf mutism were ascertained because of the interest of a physician who had suddenly become aware of the value of human genetics through a rare disease occurring in the children of two related persons. Therefore, it must be admitted that there is some bias in favor of a large number of abnormalities, and the estimates derived from

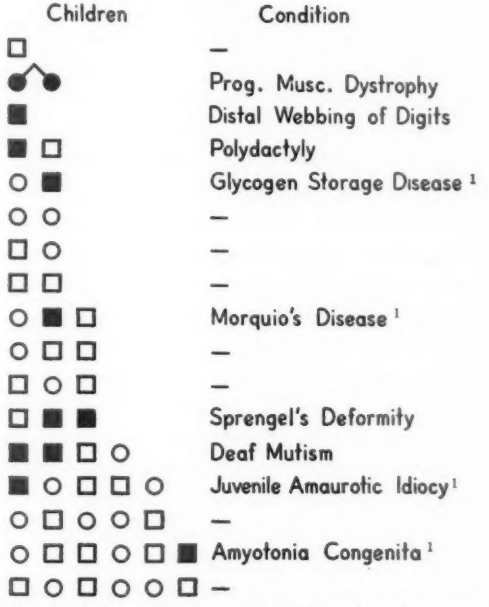

FIG. 1. Records of the live born children in 17 sibships in which the parents are first cousins

[1] The ailment indicated was the cause of admission to the hospital.

TABLE 2. THE CALCULATION OF THE AVERAGE NUMBER OF ABNORMAL RECESSIVE GENES SEGREGATING IN 17 SIBSHIPS

s	n	r	$\bar{r}$	$\bar{c}$	zn
1	3	2	0.67	2.67	0.7500
2	5	2	0.40	0.91	2.1875
3	4	2	0.50	0.86	2.3124
4	1	1	1.00	1.46	0.6836
5	2	1	0.50	0.66	1.5254
6	2	1	0.50	0.61	1.6440
	17	9			9.1029

s = sibship size.
n = number of families observed.
r = number of abnormal recessive genes observed.
$\bar{r} = \frac{r}{n}$.
$\bar{c} = \frac{\bar{r}}{z}$.
$z = 1 - 3/4^s$.

these data will tend to be high. On the other hand, a conservative attitude has been adopted toward defining conditions as recessive. Single cases of conditions for which the genetic background is not clear have been assumed to be other than simple autosomal recessives and have been omitted. The most striking instance of this is that the twins are concordant for bilateral club-foot, and the other families include three separate cases of cleft lip, one case of bilateral congenital dislocated hips, an unusual type of heart defect, and several types of mental retardation. Any of these ailments might be due to simple recessive genes in these families, but as they usually are determined in some other manner, they have been omitted from consideration here. This conservatism in the choice of abnormalities will help to correct the biases encountered in selecting these families and the slight possibility that both recessive genes were not inherited from a common ancestor.

Table 2 shows the number of families, n, of each sibship size, s, the number of independently inherited abnormalities observed, r, the mean number of abnormalities per family, $\bar{r}$ and the calculated mean number of abnormal genes for which both parents were heterozygous, $\bar{c}$. Despite the small numbers, each sibship size has produced at least one abnormality and the value of $\bar{c}$ is always greater than zero, ranging from 0.61 to 2.67. zn also appears in table 2 for the data being considered. The value of $\bar{c}$ is 9.00/9.1029, or 0.9887. The standard error of $\bar{c}$ is 0.33.

The average number of abnormal genes which are segregating among these first cousin marriages is approximately 1.0, and each pair of the common

grandparents had an average of 16 times this number of mutants, or 16. The mean number of abnormal genes per person may be estimated as about 8.

DISCUSSION

Basically, this paper is of interest as a presentation of a method, rather than a result. The formulae have the advantage of permitting the analysis of most of the pedigrees which one can obtain from human material. The choice made here, which limited the data used to first cousin marriages, was dictated by the fact that little information on matings of closer relationship was available, and the assumption that both recessive genes have been inherited from the closest common ancestors becomes too uncertain for more distant relationships. If reasonably unbiased data are available, the formulae provide a simple method for their analysis. However, the method of ascertainment of cases is exceedingly important for the proper use of these statistics. The largest bodies of such data probably consist of records based on family histories provided by unreliable informants such as students. Data collected from students would probably be inaccurate and biased against finding conditions such as mental retardation and childhood lethals.

It cannot be denied that the data on which the calculations of this paper are based are biased to some extent. The families in which an ailment was present were often detected because of the ailment. However, a relative conservatism in the definition of a recessive character and the automatic exclusion of families which have not had viable offspring because of the excessive segregation of recessive lethals should tend to balance the bias. Thus, unless there is a major amount of lethality at birth or *in utero* (and these pedigrees, which were taken with the mother as informant, do not suggest that this is so), it would appear that the estimate of eight abnormal recessive genes per person is of the right order of magnitude.

The word *abnormal* has been used in this paper because *detrimental* may well be an inappropriate term. Although some of the conditions listed were clearly lethal, Sprengel's deformity (of the scapula) and polydactyly may have no effect on viability. It is of interest that these data have given the same number as that calculated by Muller (1950) on theoretical grounds as the average number of detrimental genes per person. Despite the identity of results, it should be emphasized that the estimate developed here is affected by errors due to small numbers and inadequacies of ascertainment. The value of eight which was found here may be too high by a factor of two and may possibly be too low by almost as much. On the other hand, the *detrimental* genes discussed by Muller may include all of the mutants in the narrow scope of visibly abnormal, which was used here, plus lethals and many more mutants of much smaller outward effect (particularly in children, as Muller

specifically included genes which have a debilitating effect in old age). However, as certain of the factors which Muller has used in his calculations have been estimated by the sound application of logic, but could not be checked by facts (since we do not know how many genes there are in man or how frequently they mutate or how deleterious the average mutant is, etc.), his method of estimation may be less exact than that used here.

ACKNOWLEDGMENT

Sincere appreciation is expressed to Dr. F. C. Fraser whose care and diligence provided the records used.

SUMMARY

A method is presented by which the average number of simple recessive genes which cause rare abnormalities may be estimated by the investigation of the progeny of closely related persons. Formulae for the solution of this problem are developed and applied to data obtained from an investigation of seventeen families in which the parents are first cousins. It is calculated that these parents share an average of 1.0 abnormal recessive genes with their spouses, and their common grandparents averaged 16 abnormal genes per couple. From this it is estimated that the average person is heterozygous for eight abnormal genes.

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Hereditary Multiple Exostoses

J. FLOYD CANNON

Salt Lake Clinic, Salt Lake City, Utah

A CASE of multiple exostoses was first reported in 1837 and the first instance of multiple exostoses observed in several members of a family was in 1845. The hereditary origin of certain cases of multiple exostoses was first clearly recognized in 1890, by which time about 40 families had been described as exhibiting two or more members. In all hereditary cases subsequently described it appears that exostoses have been associated with enchondromata either in the same family or other members of the family. Concerning their mode of inheritance, the two disorders are closely related. The outgrowths from the perichondrium are not always multiple and some members may have an isolated growth. Unnoticed small outgrowths, slight deformities or confusion with rickets may obscure the heredity factor. The trait has been observed to miss a generation and pass on to the next generation through an unaffected female. A group of 765 cases with definite familial history occurring in 183 families has been assembled (1).

It has been observed to occur in 716 males (69%) and 312 females of a group of 1028 cases. It is interesting that the sex ratio in the non-hereditary type is the same as the hereditary type (1).

The age of onset of the hereditary type is usually from birth through the growth period. The abnormality is found from birth in 17 per cent of the hereditary type, and in the non-hereditary type only 4.5 per cent have the abnormality at birth (1).

The earliest, most common sites of the lesion involve the lower end of the femur and the upper part of the tibia. This is probably due to early appearance of the centers of ossification of these bones.

The number of outgrowths varies greatly. They may appear singly; as many as 1000 have been observed on one patient. The distribution is usually symmetrical. In most cases the patient is short in stature and the deformity is most marked in the forearm, with a bowing of the ulna and radius resulting from the union of these bones during the growing period. It has been observed that some patients have hyperextensibility of the joints. This finding is observed in Family 1 in this study.

It is thought the exostoses which are developing and will involve neighboring bones should be removed. During the growth period the uniting of the bones at their ends will result in bowing. In families where the trait is known

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to be present, care should be taken to remove the exostoses before deformity results.

HEREDITY IN THE PRESENT STUDY

Family 1

The mother of the present patient (Fig. 1 No. 2) died at the age of 23 years. She was short in stature and had deformity of the extremities from the multiple exostoses. The patient's sister has had no indications of the lesions being present, nor have any of her children. The patient's father and children by a second marriage are also free of the symptoms.

The patient (Fig. 1 No. 3) was a forty-one year old, white male accountant who entered with the chief complaint of multiple bony masses in the area of the left scapula. He had had no accidents.

The present complaint dates back to early childhood when the outgrowths of bone were first noted. They had decreased the rate of growth since the age of puberty. They had caused no pain until the past few weeks when the patient noted pain in the area of the left scapula. He had noted no limitation of motion, but had noted deformity in the extremities. Since early childhood he had noted hyperextensibility of the joints of the hands and feet.

Physical examination showed a thin, short male, 65½ inches tall, weighing 109 pounds. Deformities of the extremities were marked. Except for the bony outgrowths the patient was normal on physical examination.

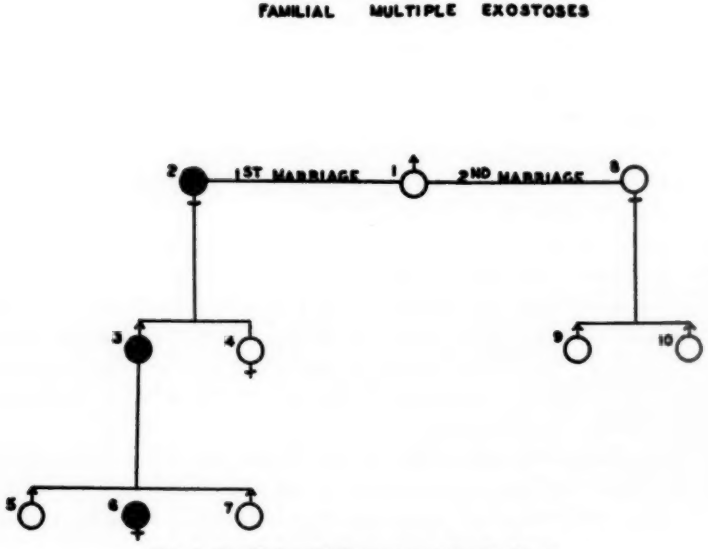
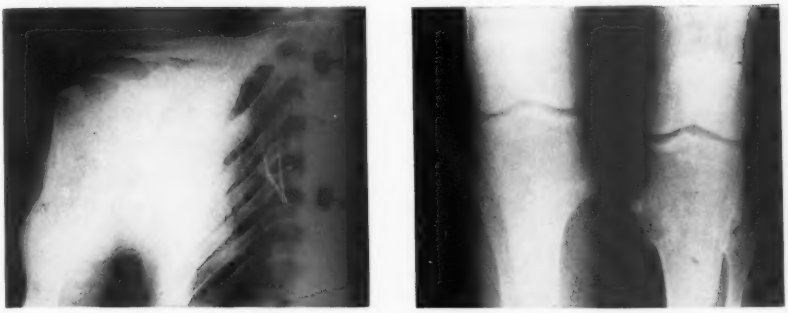


FIG. 1. Familial multiple exostoses, Family No. 1



FIGS. 2 (left) and 3 (right). Radiographs of exostoses of individual 3, Family 1

The serological test for syphilis was negative. The blood count and urinalysis were normal.

X-ray examination (Fig. 2–3) showed exostoses of the left scapula, left humerus, left clavicle, some ribs on the left, and the radius and ulna of both arms have exostoses at the distal portions. Some of the phalanges were also involved. The femurs of both legs were involved, as were the tibiae and fibulae of both legs. The right and left ilium, and right and left femur in the area of the trochanters were involved.

Two exostoses were removed from the costal surface of the left scapula. The larger measured 7 x 7 x 6 cm. in size; the other measured 6½ x 5 x 4 cm. They both presented a bony pedicle by which they had been attached to

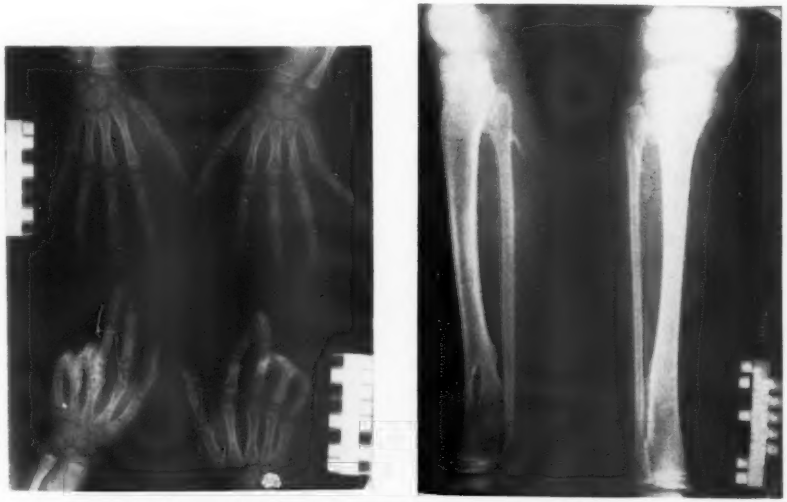


FIG. 4 (left) and 5 (right). Radiographs of exostoses of individual 6, Family 1

their parent tissue. These measured 4 cm. in diameter for the larger and 1½ cm. for the smaller. The surface was lobulated in appearance and made up of cartilage whereas the central portion was dense bone. Sections taken of the exostoses portion of the masses presented well defined hyaline cartilage. The structure was well formed and there was no evidence of malignancy.

The pathological diagnosis was osteochondromata. The clinical diagnoses were hereditary multiple exostoses and hyperextensibility of the joints of the hands and feet.

His first child (Fig. 1 No. 5) died by drowning at 2½ years. This child was free of the lesions, according to the parents.

The second child (Fig. 1 No. 6) was a six year old girl whose chief complaint was hay-fever, asthma and allergy to certain fruits. The patient and parents had noted only one bony outgrowth at the left sterno-clavicular joint. She had had hyperextensibility of the joints in the hands and feet since birth.

Her father and paternal grandmother had multiple exostoses. Her mother and brother had hay-fever, asthma and allergy to certain fruits.

Physical examination showed a thin white girl 47½ inches in height and weighing 41½ pounds. One bony outgrowth was palpable at the left sterno-clavicular joint and one at each of the distal ends of the right and especially the left femur.

The serological test for syphilis was negative. The blood count and urinalysis were normal.

X-ray examination of the head and neck revealed no exostoses.

The x-ray of the thorax revealed exostoses on the left and right scapula, left clavical at the sterno-clavicular joint, the left humerus at the proximal portion and also a small one on the shaft (Fig. 6). X-ray of the hips and femurs revealed an irregular ilium bilaterally. The femur on the right in the area of the trochanter showed a beginning exostoses. The distal portion of the right and especially the left femur presented osteochondromata. The proximal portions of the right fibula and the distal portion of the right tibia and fibula were involved, (Fig. 6). The distal portion of the left radius presented an exostoses (Fig. 5).

The clinical diagnoses were hereditary multiple exostoses, hay fever and hyperextensibility of the joints of the hands and feet.

The third child was a four year old boy (Fig. 1 No. 6) with no complaints. His father and sister have multiple exostoses and hyperextensibility of the joints of the hands and feet. His mother has hay-fever, asthma and allergy to certain foods. The patient has had hay-fever, hives, eczema and asthma. No abnormal findings were noted in the patient except for marked hyperextension of the fingers and toes.

The blood count and urinalysis were normal. The serological test for syphilis

was negative. X-ray examination revealed no bony abnormality. The clinical diagnosis was hyperextensibility of the joints of the hands and feet.

Family 2

The original patient was the fourth child in the fourth generation. She was a twenty-three year old white female salesclerk (Fig. 6 Generation IV, No. 4).

Her father and paternal grandmother had multiple exostoses, also the grandmother's father had the abnormality. The grandmother was the second wife. The progeny of the first wife, consisting of nine children, were all normal.

The patient first noted a lesion on the right arm at five years of age. She had broken her arm previously and thought the first lesion was related to the healing process. She stated that she thought the lesions were only noted after injury.

About two years before examination the patient fell while skating and injured her back. One year before examination, she noted the onset of weakness of the legs associated with increasing numbness and tingling. There was a definite decrease in the motor power of the legs. Temperature discrimination and position sense were diminished. There was a loss of pain sensation below the third lumbar vertebra. The deep reflexes were hyperactive, with a sustained ankle clonus and bilateral positive Babinski reflexes.

The blood examination and urinalysis were negative. Physical examination was negative except for the deformity present.

X-ray examination of the pelvis, with special reference to the ribs and shoulder girdle, the right femur, both upper extremities, and both hands show an extensive involvement of virtually the entire skeleton with multiple bone exostoses, of both major types, spicule and cauliflower. Fig. 7 and 8.

The right ulna is rather markedly bowed, with dislocation and deformity of

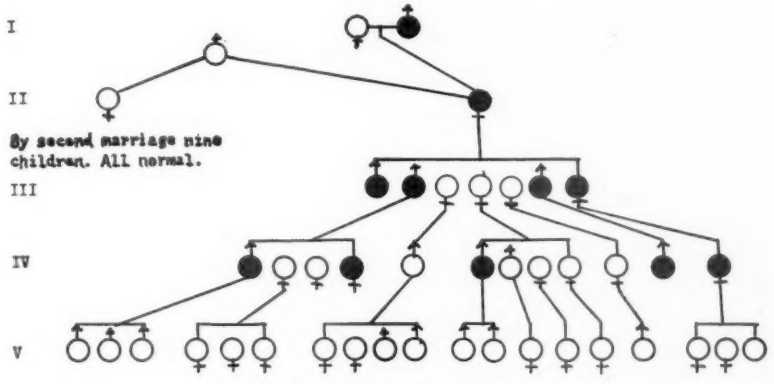


FIG. 6. Familial multiple exostoses, Family 2

FIGS. 7 (left) and 8 (right). Radiographs of exostoses of IV-4 in Family 2

the right radial head. An interesting variation is present in the hands; the third, fourth and fifth metacarpal bones are unusually short.

A spinogram demonstrated a complete block to the flow of oil opposite the tenth dorsal vertebra, with some deformity on the right side opposite the eleventh and twelfth dorsal vertebra. Later a laminectomy was done with a good result. The lesion was established to be a large osteochondroma.

Due to osteochondromatous deformity of the pelvis a cesarian section was necessary in a later pregnancy.

The diagnosis was multiple bony exostoses involving the entire skeleton visualized, of both the spicule and cauliflower type, with other bony anomalies of development.

A summary of the third and fourth generations gives some indication of how the hereditary trait is carried. In these two generations there were two unaffected males, and eight unaffected females, making a total of ten unaffected members. There were six affected males and three affected females, making a total of nine positive members. There was one unaffected female carrier who had no exostoses; however, her one son had multiple exostoses. This type of female carrier may account for the many negative females. The ratio of affected to normal in complete sibships is approximately one to one, suggesting the action of an autosomal dominant gene, probably with reduced penetrance.

This family, as in all other families so involved, shows marked variation in the severity of the abnormality.

CONCLUSIONS

1. Another two families of hereditary multiple exostoses are added to the literature.

2. Four new cases are presented, along with their x-ray findings.

3. The inheritance follows the pattern of a dominant characteristic, with incomplete penetrance in the female.

4. The outgrowths involve neighboring bones early, therefore it is thought advisable to remove the exostoses that are developing to involve other bones and thus perhaps prevent the abnormality. This type of abnormality is often seen in the radius and ulna.

5. Where the family history of the disease is present early examination and treatment are advisable.

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Tables and Nomogram for Calculating Chances of Excluding Paternity[1]

WILLIAM C. BOYD

School of Medicine, Boston University

THE CHANCES of disproving by blood grouping tests a charge of paternity brought against an innocent man were calculated several years ago by a number of authors (Hooker and Boyd, 1928; Wiener *et al.*, 1930; Koller, 1931; Zarnik, 1930). Since that time, the number of blood group systems which may be employed in such tests has greatly increased, and it is often desired to calculate the combined chances of exclusion of paternity, if certain ones of these systems are tested, and the tests in each system are made with varying degrees of completeness. A table of the results of such calculations by Fisher, for the English population, is given by Race and Sanger (1950).

If it is desired to construct such a table for a different population, with its different gene frequencies, or for the same population with a different combination of tests, or with some tests carried out with a greater or less degree of completeness, this can be done by going back to the basic relations between the probability of excluding paternity in the case of a falsely accused man, and the gene frequencies in the population.

The simplest system is that of a pair of allelic genes, one dominant. Such a system is exemplified by the "secretor" phenomenon in man, or any of the blood group systems such as MN, Kell, Duffy, or Kidd (Race and Sanger, 1950; Ruffié, 1953), when only one antiserum is available. In this case, we can only exclude paternity when the mother and alleged father belong to phenotype D− (genotype dd) and the child is of phenotype D+, where D represents the gene which causes the production of the antigen for which we can test, d is the alternative gene, and D+ represents the phenotype which is made up of genotypes DD and Dd. Then the probability P of excluding a man chosen at random from the population has been shown to be (Wiener *et al.*, 1930; Race and Sanger, 1950)

$$P_{D,d} = Dd^4 \tag{1}$$

where D stands for the frequency of the gene D and d for the frequency of the gene d.

A table of the chances of exclusion for various values of D is given in table 1. It will be noted that the probability is a maximum at $D = 0.2$, $d = 0.8$.

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TABLE 1. PROBABILITIES (P) OF PATERNITY EXCLUSION WITH A GENE PAIR D, d, GENE D DOMINANT

D	P	*D*	P	*D*	P	*D*	P	*D*	P	*D*	P
.01	.010	.16	.080	.31	.070	.46	.039	.61	.014	.76	.003
.02	.018	.17	.081	.32	.068	.47	.037	.62	.013	.77	.002
.03	.027	.18	.081	.33	.067	.48	.035	.63	.012	.78	.002
.04	.034	.19	.082	.34	.065	.49	.033	.64	.011	.79	.002
.05	.041	.20	.082	.35	.063	.50	.031	.65	.010	.80	.001
.06	.047	.21	.082	.36	.060	.51	.029	.66	.009	.81	.001
.07	.052	.22	.081	.37	.058	.52	.028	.67	.008	.82	.001
.08	.057	.23	.081	.38	.056	.53	.026	.68	.007	.83	.001
.09	.062	.24	.080	.39	.054	.54	.024	.69	.006	.84	.001
.10	.066	.25	.079	.40	.052	.55	.023	.70	.006	.85	.000
.11	.069	.26	.078	.41	.050	.56	.021	.71	.005	.86	.000
.12	.072	.27	.077	.42	.048	.57	.020	.72	.004	.87	.000
.13	.075	.28	.075	.43	.045	.58	.018	.73	.004	.88	.000
.14	.077	.29	.074	.44	.043	.59	.017	.74	.003	.89	.000
.15	.078	.30	.072	.45	.041	.60	.015	.75	.003	.90	.000

D = frequency of gene D

The gene frequencies may be estimated as $d = \sqrt{\text{D}-}$, $D = 1 - d$.

If two antisera are available, and the products of both genes can be detected, as in the case of the MN blood groups, the probability of exclusion is (Wiener, 1952)

$$P_{\text{M,N}} = mn(1 - mn) \tag{2}$$

A table[2] of the probabilities for various values of the less frequent of the two genes in such a system (called here arbitrarily N) is given in table 2. The maximum probability is reached at $m = n = 0.5$.

The frequency n is best obtained as $n = N + MN/2$, where N represents the frequency of the type positive only with anti-N and MN the type positive with both anti-N and anti-M.

In blood group systems with three allelic genes, as the ABO system, the probability depends upon the frequencies of all three genes. If we let p, q, and r represent the frequencies of the genes A, B, and O, as usual, the chances of exclusion are (Wiener *et al.*, 1930)

$$P_{\text{A,B}} = p(q + r)^4 + q(p + r)^4 + pqr^2(p + q + 2) \tag{3}$$

Since $p + q + r = 1$, there are really only two independent variables in this equation, and we can calculate the chances of exclusion in terms of r and p/q (or q/p). The results of this calculation are shown in table 3. From this table probabilities for any combination of r and p/q which is likely to be encountered can be found by double interpolation. For populations where q is greater than p we enter the table with q/p instead of p/q.

[2] A graph showing the relationship between the probabilities of exclusion and the gene frequencies for the D,d and the M,N cases is given by Cotterman (Cotterman, C. W. A note on the detection of interchanged children. Am. J. Human Genetics *3*, 363–375, 1951).

TABLE 2. PROBABILITIES (P) OF PATERNITY EXCLUSION WITH A GENE PAIR M, N, NO DOMINANCE

n	P	n	P	n	P	n	P	n	P
.01	.010	.11	.088	.21	.138	.31	.168	.41	.183
.02	.019	.12	.094	.22	.142	.32	.170	.42	.184
.03	.028	.13	.100	.23	.146	.33	.172	.43	.185
.04	.037	.14	.106	.24	.149	.34	.174	.44	.186
.05	.045	.15	.111	.25	.152	.35	.176	.45	.186
.06	.053	.16	.116	.26	.155	.36	.177	.46	.187
.07	.061	.17	.121	.27	.158	.37	.179	.47	.187
.08	.068	.18	.126	.28	.161	.38	.180	.48	.187
.09	.075	.19	.130	.29	.164	.39	.181	.49	.187
.10	.082	.20	.134	.30	.166	.40	.182	.50	.188

n = frequency of gene N (less frequent of pair)

It will be noted that for each value of the ratio p/q the probability has a maximum value. For $p/q = 1$ this maximum is 0.1999, and at this point r has the value 0.5574 (Wiener *et al.*, 1930). For other values of p/q there is also a relative maximum at some value of r, which is progressively displaced to the right as p/q increases.

The gene frequencies can be estimated with sufficient accuracy for the present purpose by the usual Bernstein formulas

$$r = \sqrt{(O)}$$
$$p = 1 - \sqrt{(O + B)}$$
$$q = 1 - \sqrt{(O + A)}$$

although if the sum $p + q + r$ deviates greatly from 1 it might be desirable to adjust the crude frequencies so obtained by the Bernstein adjustments

$$r' = (r + D/2)(1 + D/2)$$
$$p' = p(1 + D/2)$$
$$q' = q(1 + D/2)$$

where $D = 1 - (p + q + r)$.

TABLE 3. PROBABILITIES OF PATERNITY EXCLUSION WITH ABO BLOOD GROUPS

p/q (or q/p)	r							
	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
1	0.122	0.155	0.182	0.197	0.198	0.182	0.145	0.086
2	0.118	0.145	0.167	0.181	0.183	0.170	0.138	0.083
3	0.111	0.130	0.148	0.160	0.164	0.155	0.130	0.081
4	0.102	0.117	0.131	0.142	0.148	0.143	0.123	0.078
5	0.094	0.105	0.118	0.129	0.136	0.134	0.117	0.077
6	0.086	0.096	0.107	0.118	0.126	0.127	0.113	0.075
7	0.079	0.088	0.098	0.109	0.118	0.121	0.110	0.074

p = frequency of A gene, q = frequency of B, r = frequency of O

As an example of the use of the table, suppose we calculate the probability of exclusion for the blood group frequencies used in the calculations of Hooker and Boyd (1928), where $p = 0.262$, $q = 0.071$, and $r = 0.671$. In this case $p/q = 3.7$. For p/q we interpolate between the values of P for $r = 0.6$ and $r = 0.7$ to obtain $P = 0.158$, and for $p/q = 4$ we get $P = 0.144$. Interpolating between these values to obtain the probability corresponding to $p/q = 3.7$, we find $P = 0.148$. Hooker and Boyd calculated $\frac{1}{7}$ approximately. The correct value is 0.1528. (Wiener *et al.* (1930) reported for these data the erroneous value $P = 0.1434$). It is evident that the table gives results satisfactory for all practical purposes.

Determination of the subgroups of A and AB would slightly increase the chances of exclusion of paternity by the ABO groups, but there is still some uncertainty as to the laws of inheritance of these subgroups (Wiener, 1943; Race and Sanger, 1950), and in any case Wiener has calculated that the chances are only increased in this way by about 3 per cent. Therefore the application of these subgroups is not considered here.

The probabilities of exclusion are more difficult to calculate in the case of blood group systems which depend on more than three allelic genes, such as the MNS and Rh systems. However, such calculations have been made by Fisher (Race and Sanger, 1950) for representative English blood group frequencies, which are close enough to those in the USA for our present purposes. If we make use of these, we may calculate a table like that given by Race and Sanger (1950) showing the combined chances of exclusion.

We can do this by the formula

$$P_{1,2 \ldots n} = 1 - (1 - P_1)(1 - P_2) \cdots (1 - P_n) \qquad (4)$$

where $P_{1,2 \ldots n}$ stands for the combined chances of exclusion and P_1, P_2 etc. for the chances for the individual systems. For instance, if we have $P_{A,B} = 0.147$, and $P_{M,N} = 0.187$, we can write

$$P_{A,B,M,N} = 1 - (0.853)(0.813) = 1 - 0.694 = 0.306$$

The calculation can be performed by the nomogram (fig. 1). The indicator is set to $P_{A,B}$ on one scale and to $P_{M,N}$ on the other. The combined probability, $P_{A,B,M,N}$ is read off from the middle scale. By repeated use of the nomogram any number of independent probabilities can be thus combined.

For the Rh and MNS systems Fisher finds $P_{Rh} = 0.252$ and $P_{MNS} = 0.274$. We may calculate our own value of $P_{A,B}$. There is a wide choice of data for the ABO blood group frequencies for the USA, any set of which would probably be sufficiently representative. If we take the data of Boyd (1939) for Boston, we find $p = 0.236$, $q = 0.089$, $r = 0.675$, and $p/q = 2.6$. From table 3 we find $P_{A,B} = 0.165$.

For the Kell system we may take the frequency of K as 0.052, and for the

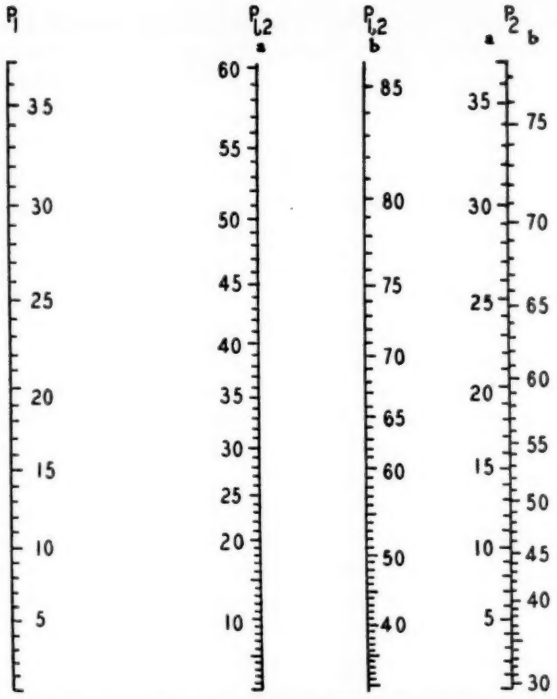

FIG. 1. Nomogram for computing combined probabilities of exclusion of paternity when two independent systems, with probabilities P_1 and P_2, are used. Use stretched thread or transparent ruler with black line. Set at value of P_1 on extreme left-hand scale, and at P_2 on extreme right-hand scale, using scale a or b depending on value of P_2. Read value of combined probability on scales $P_{1,2}$, depending on whether scale P_2 (a) or P_2 (b) was used. For example, if P_1 = 15 per cent, and P_2 = 50 per cent, we find on scale $P_{1,2}$ (b) that the combined probability = 57.5 per cent.

Duffy system Fy^a = 0.410, for the Lutheran system Lu^a = 0.039, for the secretion system S = 0.576 (Race and Sanger, 1950). For the Kidd system we may take Jk^a = 0.520 (Ruffié, 1953).

We may now proceed to construct a table showing the combined chances of exclusion, but it will make a considerable difference how complete we assume the testing for each blood group system to be. From table 1 we find that if anti-D alone is used in the Rh system, as is still common in some clinical laboratories, the chances of exclusion are only 0.018 instead of 0.252. Similarly, the chances in the Kidd system are only 0.028 if only anti-Jk^a is used, but if anti-Jk^b is also available they are increased to 0.187. It therefore seems desirable to arrange the results of the calculations into two columns, one showing the results for the simpler level of testing and the second the probabilities based on the more complete level of testing (table 4).

TABLE 4. PROBABILITIES OF AN ACCUSED MAN'S BEING EXONERATED OF A FALSE CHARGE OF PATERNITY BY BLOOD GROUP TESTS IN U.S.A.

Blood Group System	Exclusion by Each System (first level)	Combined Exclusion (first level)	Exclusion by Each System (second level)	Combined Exclusion (second level)
1. ABO	0.165	0.165	0.165	0.165
2. MNS	0.187	0.321	0.274	0.394
3. Rh	0.018	0.333	0.256	0.549
4. Kell	0.042	0.361	0.047	0.570
5. Lutheran	0.033	0.382	0.033	0.584
6. Secretion	0.019	0.394	0.019	0.592
7. Duffy	0.050	0.424	0.183	0.667
8. Kidd	0.028	0.441	0.187	0.729

Using the tables given here and the nomogram, it is a simple matter to construct similar tables showing the combined chances of exclusion based on any combination of blood grouping tests, for any population.

It will be noted that although we can calculate by equation 1 or table 1 the chances of exclusion by tests with one Rh serum (anti-D or anti-E), or any pair of Rh sera (anti-C, and anti-c or anti-E and anti-e), by equation 2 or table 2, we cannot combine these probabilities by equation 4 or the nomogram (figure 1) because these systems are not independent. However, if we do make such a combination we obtain results which are not greatly in error, which exaggerate somewhat the chances of excluding paternity. For instance, the approximate gene frequencies used by Fisher for calculating the probability in the Rh system give $C = 0.42$, $D = 0.58$, $E = 0.17$. If we assume, as did Fisher, that the usual four anti-sera, anti-C, anti-D, anti-E and anti-c, were used, we obtain $P_{C,c} = 0.184$, $P_D = 0.018$, $P_E = 0.081$. Combining by the nomogram, we obtain $P_{Rh} = 0.265$. The correct result, calculated by Fisher, is $P_{Rh} = 0.252$. Similarly Wiener (1952) shows that the result of making the similar incorrect assumption of independence in the case of the MN and Ss systems gives $P_{MNS} = 0.327$ instead of the correct 0.315 (assuming four sera, anti-M, anti-N, anti-S and anti-s, are used). This means that we can, if we wish, calculate the combined chances of exclusion for a population merely from the tables and nomogram given here, if we keep in mind that our results for MNS and Rh will be a little too high. The values obtained will be sufficiently accurate to serve as a guide.

For instance, suppose we wish to obtain the probability of exclusion of paternity in Lahore, Pakistan, where Boyd and Boyd (1954) determined the ABO, MNS, Rh, Kell, Duffy, and Kidd blood groups. They found $p = 0.184$, $q = 0.260$, $r = 0.556$. Therefore, $q/p = 1.4$, and from table 3, we find $P_{A,B} = 0.191$.

The gene frequencies of M and N can be obtained by the usual formulas

(see p. 427), and the frequency of S can be estimated as $S = 1 - \sqrt{(S-)}$. We find for Lahore $n = 0.427$, $S = 0.299$. The combined probabilities, making the incorrect assumption of independence, give $P_{MNS} = 0.244$, which is doubtless somewhat too high.

The chances of exclusion by the Rh system can be obtained similarly by combining the chances from the C,c; D,d; and E,e pairs. If four sera, anti-C, anti-D, anti-E and anti-c, are used, the C,c pair gives three distinguishable phenotypes, like MN, and we find the chances of exclusion in table 2. The frequency of C can be obtained as CC + Cc/2. The D,d and E,e pairs behave like a simple pair with dominance, and the chances of exclusion can be found in table 1. The frequency of D is calculated as $1 - \sqrt{(D-)}$, and $E = 1 - \sqrt{(E-)}$.

We find $C = 0.619$, $c = 0.381$, $D = 0.753$, $E = 0.110$, and from tables 1 and 2, we find $P_{C,c} = 0.180$, $P_D = 0.003$, $P_E = 0.069$. Combining, we find $P_{Rh} = 0.238$, which again is doubtless somewhat too high.

From the results of the Kell, Kidd and Duffy tests we find $K = 0.084$, $Jk^a = 0.481$, $Fy^a = 0.524$. Since only one serum was used for each system, we find from table 1 the chances of exclusion by these systems to be $P_K = 0.059$, $P_J = 0.035$, $P_F = 0.029$.

Combining all these probabilities, we find the combined chances of exclusion in Lahore, using the sera employed by Boyd and Boyd, are $p_{ABMNSRhKJF} = 0.588$, which is high by perhaps a few per cent, but suffices to give the approximate chances of exclusion in this population, using merely these six blood group systems at the level of testing employed by Boyd and Boyd.

If anti-k, anti-Jk^b and anti-Fy^b sera had also been available, the combined chances would be computed as 0.714.

SUMMARY

Tables are presented for calculating the chances of excluding paternity of a wrongly accused man by blood group tests, and a nomogram is given for combining such chances. Typical calculations are given.

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A Familial Study of Gastric Carcinoma[1,2]

GEORGE W. HAGY

Southwestern Medical School of the University of Texas, Dallas, Texas

INTRODUCTION

THE HIGH INCIDENCE and mortality rate of gastric carcinoma supply a need for more detailed studies which may offer some explanation of the causal factors of this type of cancer. The significance of heredity has not been determined in gastric cancer. Strong (1946) pointed out that the large number of cancer types which appear in man may be the result of the great variability of his hereditary constitution, influenced by continuous contributions from diversified ancestries. Jacobsen (1946) stated that if heredity was influential in determining the development of a particular type of human cancer, a significantly higher proportion of that type of cancer would be expected among the relatives of cancer patients than among the relatives of a suitable control group, or in the general population.

Previous familial studies of gastric cancer have suggested that there is a higher frequency of cancer among the relatives of gastric carcinoma patients. Wassink (1935) reported that mortality from cancer was considerably higher among the relatives of patients affected with gastric cancer or rectal cancer than among members of the general population. Denk (1939) found in Austria that gastric cancer occurred more frequently in relatives of gastric cancer patients than in the general population. State, Varco, and Wangensteen (1947) observed that the incidence of gastric cancer among relatives of 200 patients with gastric cancer was higher although not to a degree of statistical significance, than the frequency found among relatives of control groups. Mosbech (1953) compared the incidence of gastric cancer in the relatives of 234 patients with pernicious anemia, in the relatives of 226 control patients without pernicious anemia, and in the general population of Denmark. He found that mortality from gastric cancer was significantly higher for the relatives of pernicious anemia patients than for control relatives or the general population, while there was no significant difference in the incidence of cancer of other sites. Gardner, Woolf, and Shaffer (1953) report that in a preliminary study of gastric cancer in Utah the incidence of this disease is 2½ times greater among the parents and sibs of gastric cancer patients than in the general

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[2] Presented before the American Society of Human Genetics, Boston, Mass., December 29, 1953.

population, while cancer at other sites occurs among these individuals with approximately the frequency found in the general population. Macklin (1953) has found similar results in a study of an Ohio population, observing a frequency of gastric cancer 2½ times greater among relatives of gastric cancer patients than would be expected in random population samples.

Individual family histories have been reported which indicate a strong tendency for localization of cancer of the gastro-intestinal tract in the members of a single family group and give presumptive evidence for an inheritable organ-specific predisposition to cancer (Hauser and Weller, 1936; Gardner and Stephens, 1950; Woolf and Gardner, 1950; Gardner and Woolf, 1952).

Studies of twins have also given suggestive evidence that heredity is an important agent in the development of gastric cancer. Militzer (1935) reported the case histories of monozygous twins (males) who had identical symptoms and almost simultaneously developed gastric carcinomas; the tumors were symmetrically located in the stomachs and had marked histological similarity. Macklin (1940) and Von Verschuer and Kober (1940) reported a greater localization of gastric cancer in monozygous than in dizygous twin pairs.

In the present study a preliminary investigation has been completed on the frequency of cancer among the relatives of patients who have been treated for gastric carcinoma and among the relatives of control patients who do not have any type of cancer.

MATERIALS AND METHODS

Each gastric carcinoma proband underwent surgery and was proven to have gastric carcinoma by microscopic study of the neoplastic tissue. Each control proband had had a recent physical examination, and no evidence of cancer was found at the time of examination.

Personal interviews with probands were taken through the consent of the patient and the patient's physician. Data were recorded on the personal habits, eating habits, and family histories of the patient. In this report only data gathered on the family histories are given.

Detailed information was requested on the following relatives of each proband: children, sibs, parents, parents' sibs, and grandparents. All illnesses, operations, and causes of death of these relatives and their children were considered.

A group heterogeneous for health factors were used for controls. Some control probands were being treated for diabetes; others were being treated for or had had tuberculosis, duodenal ulcers, heart conditions, or arthritis. Some did not have any illness.

Permission was requested from probands to follow-up their family histories by contacting their relatives for additional information. Letters were sent to

relatives requesting data about their own illnesses as well as illnesses or operations of other members of the family.

Efforts were made to verify all cases of cysts, tumors, or cancers reported by the proband and his relatives. The pathological or clinical diagnosis of a condition was requested from physicians and hospitals, and if the individual was deceased, the cause of death was requested from the bureau of vital statistics. Individuals who were reported to have died of "stomach trouble" or other conditions which may have proven to be cancerous also were investigated through these sources.

RESULTS

Data have now been collected on 106 probands with gastric carcinoma and on 60 control probands. These individuals were separated by race into three groups: American "whites," Negroes, and Mexican-Americans. These groups were felt to differ genetically as well as in dietary habits, so they have been considered separately. The gastric carcinoma group includes 86 American "whites" (65 males, 21 females), 12 Negroes, and eight Mexican-Americans. The control group includes 58 American "whites" (42 males, 16 females) and

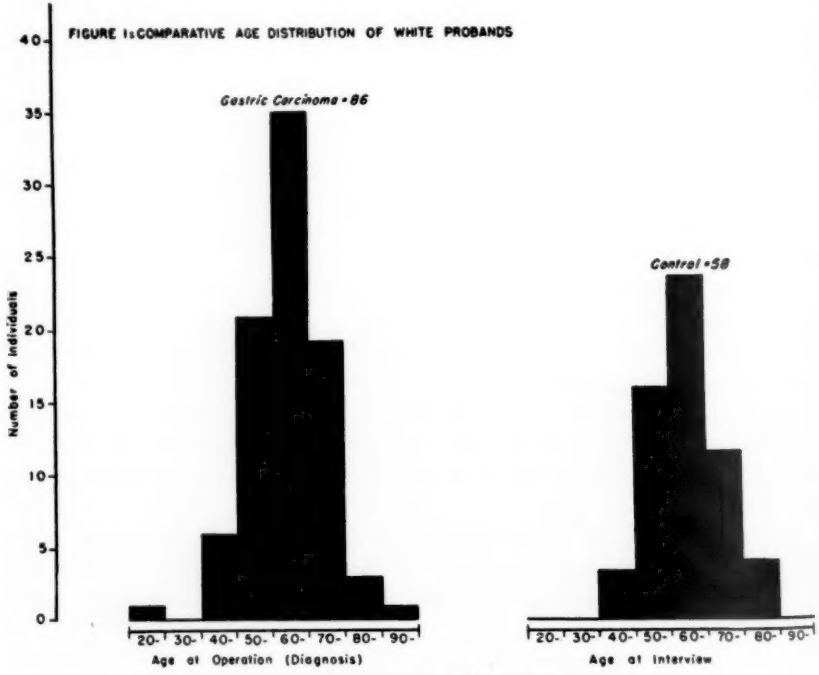

FIG. 1. Comparative age distribution of white probands

two Mexican-Americans. Statistical comparisons have been made only on data given by "white" probands in the gastric carcinoma and control groups. These two groups are comparable by age, sex, socio-economic status, marital status, religious denomination, native extraction, and order of birth.

Age Distribution of Probands

The range for age at diagnosis (age at surgery) among the stomach carcinoma probands was from 27 years to 91 years, and the average age at diagnosis was 62.6 years. The average age at interview of the control probands was 64.4 years. A comparison of the age distributions of probands is given in figure 1.

Age Distribution of Relatives

The age distribution of the relatives of the gastric carcinoma and control probands should be comparable before a hereditary tendency for cancer is tested. If one series contains a large number of relatives who have not reached the susceptible cancer age while the other series does not, an observed difference in the incidence of a given type of cancer may be explained by the age difference alone.

Comparisons between each series have been made for relatives of the relationships given in Table 1, using the ($r \times 2$) method (Goulden, 1952) as a test for homogeneity. These categories of relatives contain members who may have had the opportunity to pass the cancer age of the proband and who are

TABLE 1. COMPARISON OF THE AGE DISTRIBUTION FOR CORRESPONDING GROUPS OF RELATIVES OF GASTRIC CARCINOMA PROBANDS AND CONTROL PROBANDS

Relationship	Number of Relatives		($r \times 2$) Table*		
	Cancer series	Control series	(f)	x^2	P
Brothers	237	139	7	4.824	<.70–>.50
Sisters	223	127	7	13.797	<.10–>.05
Fathers	79	57	4	3.433	<.50–>.30
Mothers	80	57	4	2.988	<.70–>.50
Maternal Uncles	110	74	4	5.598	<.30–>.20
Maternal Aunts	99	97	4	12.240	<.02–>.01
Paternal Uncles	93	83	3	2.420	<.50–>.30
Paternal Aunts	85	66	3	3.202	<.50–>.30
Maternal Grandfathers	30	36	2	0.960	<.70–>.50
Maternal Grandmothers	24	36	2	0.954	<.70–>.50
Paternal Grandfathers	13	28	2	5.730	<.10–>.05
Paternal Grandmothers	21	24	2	1.868	<.50–>.30
Total Number	1094	824			

* Method outlined in Goulden, C. H. 1952. *Methods of Statistical Analysis*. New York: John Wiley and Sons. 2nd edition. p. 371.

of a fairly close degree of relationship to the proband. Only full blood relatives of the probands have been considered in these comparisons. Relatives who could not be classified into a given age group were omitted. These included 11 brothers, 4 sisters, 6 fathers, and 5 mothers of the immediate relatives of gastric carcinoma probands and 3 brothers, 3 sisters, 1 father, and 1 mother of the immediate relatives of control probands. It was not possible to complete the family history of one gastric carcinoma proband, and his relatives are not included in these tabulations.

More exact data on the living age or age at death of sibs and parents are known. These relatives were divided into five year age groups. The other relatives were usually more separated from the probands and often only their approximate age could be stated, so that a ten year age grouping was used for a comparison of all other relatives. Many probands were not able to give sufficient information on their grandparents who had been deceased for many years.

Chi square values were calculated from the ($r \times 2$) tables. These values are dependent on the method in which the data are grouped into classes. No individual class should contain less than five individuals since the Chi square distribution is calculated on methods of approximation. The total number of relatives considered in some categories was small, and their division into five or ten year age groups gave some classes which contained less than five individuals. Therefore, it was necessary to combine age groups in some of the calculations made in Table 1. The degrees of freedom, (f), are determined as one less than the number of age classes which were used. The probability value, P, was determined by applying the calculated Chi square value with the appropriate degrees of freedom to the Tables of Fisher and Yates.

Statistical agreement was found for each relationship except the maternal aunts who showed only doubtful agreement. However, even in this case there was no definite disagreement, and we feel justified in comparing the gastric carcinoma and control series directly for the incidence of cancer reported among these relatives.

Cases of Cancer Reported in Relatives of Probands

In the gastric carcinoma series 66 relatives and in the control series 46 relatives (whose age distributions have been tested) were reported to have some type of cancer.

Records available to us for tracing affected relatives were from physicians, hospitals, and death certificates. Not infrequently such records had not been kept or could not be found, particularly if the individual had been treated over two or three decades ago. The reliability of death certificates may also be questioned. It has been possible to verify by at least one of these methods 65.7% of the cases of cancer reported in relatives of the gastric carcinoma

series, but only 50.0% of the cases of cancer reported in relatives of the control series.

The other relatives (34.3% in the gastric carcinoma series and 50.0% in the control series) who are included as cancer cases but for whom no confirmatory record could be found, have been reported to us by several members of their family. We hope that it will be possible to obtain additional data on some of these individuals which will enable us to locate more specific information.

When reports from relatives were conflicting about the presence of cancer in an individual, and no record could be located on the individual, the case was omitted from the data. Four relatives in the gastric carcinoma series and seven relatives in the control series were omitted because of insufficient information. None of these omitted cases was reported as gastric cancer.

Cases of cancer in relatives of gastric carcinoma probands are given by site and by relationship in Table 2. Four of the 66 relatives have had more

TABLE 2. CANCER BY SITE AND BY RELATIONSHIP REPORTED AMONG RELATIVES OF GASTRIC CARCINOMA PROBANDS

Site	B	S	F	M	MU	MA	PU	PA	MGF	MGM	PGF	PGM	Total—%
Stomach	2	2	3[c]		1		1	1		1	1	1	13— 19.7
Intestine	1	2			2[d]	2							7— 10.6
Rectum	1				2[d]				1				4— 6.1
Only G.I. Tract Specified		1			1								2— 3.0
Liver	2	1						1					4— 6.1
Pancreas					1								1— 1.5
Prostate Gland	1		1		1								3— 4.6
Breast		4[a]								1			5— 7.6
Ovary		3[a]											3— 4.6
Uterus (Fundus)		2[b]		1						1			4— 6.1
Cervix uteri		3											3— 4.6
Bladder		1											1— 1.5
Jaw Bone			1										1— 1.5
Mouth											1		1— 1.5
Throat			1										1— 1.5
Lip	1						1						2— 3.0
Skin	2	3[b]	1[c]			1		3				1	11— 16.7
Leukemia	1												1— 1.5
Polycythemia vera				1									1— 1.5
Unspecified or Indefinite								1		1			2— 3.0
Total Sites	11	22	7	2	8	3	2	6	1	4	2	2	70—106.2
Number of Individuals	11	20	6	2	7	3	2	6	1	4	2	2	66—100.0

Symbols: B—Brothers, S—Sisters, F—Fathers, M—Mothers, MU—Maternal Uncles, MA—Maternal Aunts, PU—Paternal Uncles, PA—Paternal Aunts, MGF—Maternal Grandfathers, MGM—Maternal Grandmothers, PGF—Paternal Grandfathers, PGM—Paternal Grandmothers.

Four individuals had more than one primary site of cancer; each site in these individuals is designated by the same symbol, as (a), (b), (c), or (d).

than one primary site of cancer, so that the total number of sites considered is 70. The stomach and skin are the predominant sites of cancer reported among these relatives. Four relatives have been placed in unspecified groups. Two of the four, a sister and a maternal uncle, are known to have had cancer of the stomach or colon and have been placed in the classification "only gastrointestinal tract specified." Also, a paternal aunt is reported to have died of cancer of the stomach or "female organs" and a maternal grandmother is reported to have had cancer of the stomach or liver. The death record in the latter case reported "cancer of omentum." Therefore, it is possible that four other relatives in the gastric carcinoma series had cancer of the stomach and that the frequency of this site is even higher in the gastric carcinoma series than we are reporting.

Cases of cancer in relatives of control probands are given by site and by relationship in Table 3. Two of the 46 relatives have had more than one primary site of cancer. Only skin cancer is the outstanding site among these relatives. Information known on the five relatives included in the unspecified or indefinite group is as follows: The death of a maternal aunt, reported by

TABLE 3. CANCER BY SITE AND BY RELATIONSHIP REPORTED AMONG RELATIVES OF CONTROL PROBANDS

Site	B	S	F	M	MU	MA	PU	PA	MGF	MGM	PGF	PGM	Total—%
Stomach					1	1	2[b]						4— 8.7
Intestine	1			2									3— 6.5
Rectum		1											1— 2.2
Liver		1											1— 2.2
Pancreas	1	1											2— 4.4
Prostate Gland					1		2						3— 6.5
Breast				1				3					4— 8.7
Uterus (Fundus)		2[a]		1		1		1					5— 10.9
Bladder		1[a]				1							2— 4.4
Tongue	1												1— 2.2
Throat	1									1			2— 4.4
Lip			2								1		3— 6.5
Skin	1	2	2				1[b]		1	1			8— 17.4
Malignant Melanoma		1											1— 2.2
Leukemia	1												1— 2.2
Hodgkin's Disease		1											1— 2.2
Sarcoma Bone	1												1— 2.2
Unspecified or Indefinite						2	1			1		1	5— 10.9
Total Sites	7	10	4	4	2	5	6	4	1	3	1	1	48—104.7
Number of Individuals	7	9	4	4	2	5	5	4	1	3	1	1	46—100.0

Symbols: B—Brothers, S—Sisters, F—Fathers, M—Mothers, MU—Maternal Uncles, MA—Maternal Aunts, PU—Paternal Uncles, PA—Paternal Aunts, MGF—Maternal Grandfathers, MGM—Maternal Grandmothers, PGF—Paternal Grandfathers, PGM—Paternal Grandmothers.

Two individuals had more than one primary site of cancer; each site in these individuals is designated by the same symbol, as (a) or (b).

the proband to be due to cancer, has been verified by the death certificate as "secondary carcinoma of the uterus." The hospital record of a paternal uncle, reported to have died of "internal cancer" in 1915, states only that the patient was admitted in 1914 for "gallstones and bladder trouble"; no additional information is known on this patient. A maternal grandmother is reported to have died of cancer of the "female organs" and a maternal aunt and paternal grandmother are stated to have died of cancer of unknown sites.

Incidence of Cancer in the Gastric Carcinoma and Control Series

In the gastric carcinoma series, 66 out of 1,094 relatives were affected with cancer. This is a cancer frequency of 6.0% among these relatives. The primary site of cancer in 13 of these individuals is reported as stomach, giving a frequency of 1.2% for gastric cancer.

In the control series, 46 out of 824 relatives were affected with cancer, yielding a frequency of 5.6%, which is nearly as great as the frequency of cancer in relatives of gastric carcinoma probands. However, the frequency of gastric cancer among the relatives of control probands is less than half that in the gastric carcinoma series. Only four relatives in the control series are reported with gastric cancer, giving a frequency of 0.5%.

The term "gastric cancer," rather than "gastric carcinoma," is used to refer to relatives who are included in this group, since it has not been possible to determine the pathological type of each case of gastric cancer (carcinoma or sarcoma).

The difference of gastric cancer in the two series, 1.2% to 0.5%, is not significant by statistical test and could occur by chance alone (1.71 times the standard error of the difference).

If the four relatives in the gastric carcinoma series who have been reported possibly to have had gastric cancer are added to the 13 relatives already considered affected with gastric cancer, the frequency of gastric cancer is then 1.6%. This frequency, compared to the 0.5% frequency in the control series is significantly greater by statistical test and might be due to factors other than chance (2.38 times the standard error of the difference). With the small numbers involved and the trend that is observed with gastric cancer, a difference of one or two relatives can alter the results for significance or nonsignificance. Therefore, the two series were compared to a larger sample of data representative of the general population.

Morbidity and Mortality Data

Either morbidity or mortality data may be used for comparisons of the frequency of cancer in the general population to the frequency observed in the proband materials. Morbidity data are the desired material since they are expected to include both living and deceased cases of cancer and should give

a more accurate estimate of the occurrence of this disease. In the proband materials cancer in both living and deceased relatives is considered. At the present time morbidity data have not been collected in full for the state of Texas. They are available from a study made by Macdonald (1948) for the state of Connecticut. Her study covers a period from 1935–1946.

At the time of the investigation the most recent tabulation of mortality data for Texas, 1951, was also used. These data give an estimate of the number of deaths caused by cancer in Texas during 1951.

The 1940 Connecticut population and the 1950 Texas population were compared and found generally to follow the same age distributions except for the youngest part of the populations. A larger percentage of the Texas population occurred in the "under ten year" age groups than in the Connecticut

TABLE 4. FREQUENCY OF CANCER OF DIFFERENT SITES AMONG MALES AND FEMALES IN RELATIVES OF GASTRIC CARCINOMA PROBANDS, RELATIVES OF CONTROL PROBANDS, MORBIDITY DATA OF CONNECTICUT (MACDONALD, 1935–1946), AND MORTALITY DATA OF TEXAS (1951)

Site	66 Relatives of Gastric Carcinoma Probands		46 Relatives of Control Probands		Connecticut Morbidity Data		Texas Mortality Data	
	No.	%	No.	%	No.	%	No.	%
Breast	5[a]	7.6	4	8.7	5244	13.9	574	7.8
Esophagus	0	—	0	—	567	1.5	115	1.6
Stomach	13[b]	19.7	4[e]	8.7	2994	7.9	696	9.5
Intestine	7[c]	10.6	3	6.5	4012	10.6	680	9.3
Rectum, Anus	4[c]	6.1	1	2.2	1954	5.2	220	3.0
Liver, Gallbladder, and Ducts	4	6.1	1	2.2	632	1.7	365	5.0
Pancreas	1	1.5	2	4.4	738	2.0	351	4.8
Peritoneum and Unspecified Digestive Organs	3	4.6	0	—	220	0.6	48	0.7
Skin	11[bd]	16.7	8[e]	17.4	3597	9.5	120	1.6
Lip	2	3.0	3	6.5	630	1.7	11	0.2
Upper Alimentary Tract*	2	3.0	3	6.5	1030	2.7	141	1.9
Respiratory System†	0	—	0	—	1856	4.9	834	11.4
Male Genitals	3	4.6	3	6.5	1990	5.3	424	5.8
Uterus (including Cervix)	7[d]	10.6	5[f]	10.9	3844	10.2	574	7.8
Ovaries	3[a]	4.6	0	—	1173	3.1	170	2.3
Other Female Genitals	0	—	0	—	138	0.4	12	0.2
Urinary Tracts	1	1.5	2[f]	4.4	1679	4.4	306	4.2
Brain and Central Nervous System	0	—	0	—	664	1.8	151	2.1
Lymphatic and Hematopoietic Tissues	2	3.0	2	4.4	1625	4.3	669	9.1
Others and Unspecified Sites	2	3.0	7	15.2	3276	8.7	859	11.7
Totals	70	106.2	48	104.5	37863	100.4	7320	100.0

The following sites are included in (*)—Mouth, palate, gum, tongue, pharynx, nasopharynx; (†)—Larynx, trachea, bronchus, lung, mediastinum, thoracic organs. Four relatives in the gastric carcinoma series and two relatives in the control series had more than one primary site of cancer; each site in these individuals is designated by the same symbol, as (a), (b), (c), (d), (e), or (f).

population. However, during these age periods the incidence of cancer is much lower than for the succeeding age periods, so that this difference is not of great significance. Since the two populations have approximately the same percentage segments susceptible to cancer above the ten year age level, the morbidity data of Connecticut were compared with the mortality data of Texas and the observed familial incidences (Table 4).

Comparison of Familial Data with Morbidity and Mortality Data

When the gastric carcinoma series was compared with the morbidity or mortality data, two sites of cancer, the stomach and skin, occurred with a high frequency among male and female relatives. When similar comparisons were made for the control series, skin cancer was the only type which was strikingly higher.

The method used for the following statistical considerations was a comparison of the percentage difference with the standard error of the difference. The incidence of gastric cancer in male and female relatives of gastric carcinoma probands was more than would be expected through chance alone as based on the frequency in the general population. However, when the relatives of gastric carcinoma probands were separated by sex and the frequency of gastric cancer was compared independently to that frequency of the corresponding sex in the morbidity or mortality data, the results were not statistically significant.

Statistical tests on the frequency of skin cancer were all insignificant except for one instance. The females of the gastric carcinoma series have a significantly higher incidence of skin cancer than females in the morbidity data. Comparison of the female relatives in the gastric carcinoma and control groups shows that there are no important differences in the frequencies of skin cancer observed in these two groups. Hueper (1952) pointed out that environmental factors play an important role in the development of skin cancer, so that it is difficult to evaluate the effect of hereditary factors.

Other sites of cancer do not differ significantly when tested together. The control group does not differ significantly by statistical test from the morbidity data for any site of cancer.

The incidence of cancer of the gastro-intestinal tract was considered, due to the difficulty in classifying some cases of cancer. Only the part of the gastro-intestinal tract lined by columnar epithelium was included in this classification. The following sites were totalled: stomach, small intestine, large intestine, and rectum (Table 5). This grouping allows the inclusion of the two relatives in the gastric carcinoma series who had cancer reported as stomach or colon. However, another relative in the gastric carcinoma series had two primary gastro-intestinal sites, the intestine and rectum, and he has been counted only once in these data.

TABLE 5. FREQUENCY OF CANCER OF THE GASTRO-INTESTINAL TRACT* IN RELATIVES OF GASTRIC CARCINOMA PROBANDS, RELATIVES OF CONTROL PROBANDS, MORBIDITY DATA OF CONNECTICUT (MACDONALD, 1935–1946), AND MORTALITY DATA OF TEXAS (1951)

Affected Group	♂♀		♂		♀	
	No.	%	No.	%	No.	%
Relatives of gastric carcinoma probands	25	37.9	15	51.7	10	27.0
Relatives of control probands	8	17.4	4	20.0	4	15.4
Connecticut morbidity data (1935–1946)	8932	23.6	5047	29.0	3885	19.0
Texas mortality data (1951)	1596	21.8	836	22.6	760	21.0

* Includes cancer of the stomach, small intestine, large intestine, and rectum.

The frequency of cancer of the gastro-intestinal tract in males and females of the gastric carcinoma series was significantly higher by statistical test than the frequency reported in the control material, the morbidity data, or the mortality data. When considered by sex, the frequency was significantly higher in males but not in females when each was compared to the males and females respectively of the control data or the data of the general population.

Gastric cancer affects primarily an older age group. The youngest proband in the gastric carcinoma series was a woman aged twenty-seven years at the onset of gastric carcinoma.Therefore, twenty-five years was selected as the earliest age for onset of gastric cancer in the gastric carcinoma and control series, and only relatives who lived at least twenty-five years were considered. This included 980 relatives in the gastric carcinoma series and 748 relatives in the control series. All relatives reported affected with gastric cancer in each series were past twenty-five years of age. Thus, the frequency of gastric cancer in relatives who reached this "cancer age" was 1.33% in the gastric carcinoma series and 0.53% in the control series. This tabulation gave an increased incidence of gastric cancer in the relatives in each series; however, the difference was not significant.

The number of cases of gastric cancer were distributed through all levels of relationship, and there was no particular concentration at any one level. The observed number of cases in each series was too small to test for a significant increase in gastric cancer in any level of relationship in the gastric carcinoma and control series.

During the familial study a physician referred us to a patient who did not have cancer but who stated that most of her relatives had died of cancer. This history has been followed separately from the gastric carcinoma and control series and is still under investigation. At present there is a reported frequency of gastric cancer among this patient's relatives which is nearly four times higher than is present in the relatives of the gastric carcinoma probands and over nine times higher than is present in the relatives of the control pro-

bands. This history gives evidence for a strong localization factor for gastric cancer in one family group.

DISCUSSION

The selection of a control group is an immediate problem in human genetic work. It has been difficult to match with the gastric carcinoma probands control probands who are of the same age distribution and are enjoying normal health. Jacobson (1948) reported that there was apparently some type of association between cancer and other conditions, as diabetes, tuberculosis and syphilis. Some conditions might also predispose against the development of cancer. Selection of patients who are affected with one particular disease may be inadequate for a control group. For this reason the control series used in this study was selected from among a group of patients heterogeneous for health factors.

Both the gastric carcinoma and control materials have a higher frequency of all types of cancer than is present in the general population. The relatives of the control probands have nearly as high a frequency of cancer of all sites as the relatives of the gastric carcinoma probands. Murphy (1952) found in a familial study of cancer of the uterus a higher frequency of cancer of all sites among the relatives of his control probands.

We may conclude from the present data that there appears to be a greater tendency to find gastric cancer among the relatives of a patient with gastric carcinoma than among the relatives of an individual who does not have gastric carcinoma. This series of data does not allow for a hereditary factor for localization of gastric carcinoma to be decided. The increase of gastric cancer among the relatives of the gastric carcinoma probands can be credited to chance alone, but the data are not clear-cut enough to rule out the possibility of a hereditary influence.

The present data may become significant by statistical test when larger sample sizes are compared, if the trend of gastric cancer now noted in this study is maintained. State, *et al.* (1947) also reported a trend in the frequency of gastric cancer among the relatives of gastric cancer probands as compared to the frequency observed among the relatives in control groups.

Wassink (1935) suggested that a disposition of the organs was due to a disposition of tissues, and that a genetically conditioned tendency to the development of cancer in cylinder epithelium lining the gastro-intestinal tract might give rise to cancer in the stomach as well as the colon. Consideration of "cancer of the gastro-intestinal tract" allows the inclusion of some cases of cancer uncertain for site among relatives in our gastric carcinoma series. By this grouping there is an increase significant by statistical test in the frequency of cancer of the gastro-intestinal tract in both male and female

relatives together and in male relatives alone in the gastric carcinoma series, in comparison to the frequency of cancer of the gastro-intestinal tract in similar individuals of the control series, morbidity data, or mortality data. However, even by this grouping there is no significant statistical difference in the frequency of cancer of the gastro-intestinal tract observed among female relatives of the gastric carcinoma probands when compared to the frequency observed in female relatives of the control probands, or females of the morbidity data or mortality data.

Difficulties in verifying reported cases of cancer have been encountered in both the gastric carcinoma and control groups. Only a limited faith can be placed in death records which have been used as one source of confirmation of cases of cancer. It has been possible for us to verify a greater proportion of the cancer cases reported among relatives in the gastric carcinoma series (65%) than in the control series (50%). For this reason more reliability may be placed on the incidence of cancer in our gastric carcinoma series. The same methods have been used to trace the relatives in each series, and the data have been evaluated in the same way. Similar problems are encountered in tracing relatives in each series. When patients of an older age group are used as probands, it is often difficult to trace back relatives more than one generation. However, the difference that is observed in the data for an increased frequency of gastric cancer in the gastric carcinoma series assumes more importance when one realizes that the series have been treated and evaluated in the same way and are both subject to the same shortcomings.

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Parental Stature and Birth Weight

R. H. CAWLEY, THOMAS McKEOWN AND R. G. RECORD

Department of Social Medicine, University of Birmingham

In 1938 Walton & Hammond described the results of reciprocal Shire-Shetland crosses effected by artificial insemination. They showed that the weight of the foal of Shire dam and Shetland sire was about the same at birth as that of the foal of pure Shire parents, and the weight of the foal of Shetland dam and Shire sire was no greater than that of the foal of pure Shetland parents. Numbers of observations were very small, but the differences exhibited were so striking that it can hardly be doubted that the weight of the foal at birth was more highly correlated with the weight of the dam than with the weight of the sire. Walton & Hammond attributed this result to the uterine environment, and noted that after weaning "foals from the Shire mares (Shetland sires) grew much less rapidly than pure Shire foals, and the foals from the Shetland mares (Shire sires) grew much more rapidly than pure Shetlands".

In rabbits, similar results were reported by Robb (1929) on data provided by Castle who crossed Flemish Giant and Polish breeds. Hybrid animals from Giant does and Polish bucks were almost as large at birth as pure bred Giants; unfortunately Polish does and Giant bucks were not mated. Differences in growth rate were exhibited after birth, and the weight of mature hybrid animals was about midway between weights of the pure breeds.

In man, correlations between size of parents and size of offspring at birth have been examined by Lennér (1943), who found only trivial differences (a) between correlations of birth weight with mother's weight (0.19) and birth weight with father's weight (0.18), and (b) between correlations of birth length with mother's height (0.20) and birth length with father's height (0.21). When corrected for height of the other parent correlations were lowered slightly, but still indicated that the size of the child at birth is about equally affected by the size of each parent.

A preliminary inspection of a somewhat larger series of our own gave a different result, more consistent with the observations derived from the Shire-Shetland cross. We have therefore examined more exhaustively correlations at birth, and in the two years after birth, between the size of a child and the size of its parents. In another communication (McKeown & Record, 1954) we enquire to what extent these correlations are modified by changes in the prenatal environment, in particular those associated with litter size and birth order.

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MATERIAL

The observations which follow are based upon material from two sources.

(*a*) *Smethwick Data*

The data were obtained in an investigation of pregnancies of all mothers domiciled in the County Borough of Smethwick, whose children were born between April 1st, 1949 and March 31st, 1950. An attempt was made to record weight and height of both parents, and infant weight at birth, and at 3, 6, 9, 12 and 24 months after birth.

Mother's weight and height were measured at the first antenatal attendance. Father's weight and height were obtained by asking the mother, who gave values in some cases at once, and in other cases after consulting her husband. Infant birth weights were recorded in hospital to the nearest ounce, and at home to the nearest quarter pound; weights after birth were taken to the nearest ounce either at a welfare clinic, or at home if the child was not brought to a clinic within a few days of the appropriate date.

In view of the methods used, it seemed to us that we could accept the observations on the mother as being reasonably reliable. There is evidently a considerable error in observations on the father, particularly in the case of weight, and we have therefore made no use of father's weight. Distribution of father's height showed grouping, as might be expected, notably at 66, 68, and 70 inches. Our justification for regarding heights as being sufficiently accurate for our purpose is that they gave results which agree well with those based on the Birmingham enquiry ((b) below) in which heights of fathers were measured.

In the year under consideration there were 1,327 Smethwick births, which included 38 twins. Of the 1,289 singletons, 23 were stillborn, 23 died during the first month, and 1,243 were alive at one month.

(*b*) *Birmingham Data*

Experience of the Smethwick enquiry encouraged us to attempt to assemble another series in which we could verify the findings on data from an independent source, and explore the influence of placental size on the correlation between infant weight and parental height. We have therefore extracted the following information from records of the Birmingham Maternity Hospital for the years 1946 and 1948–50: birth weight, placental weight, birth rank, sex and duration of gestation (recorded as the period of amenorrhoea). During the 4 years there were 7,341 single births; the requisite data were complete in respect of 4,931.

In order to eliminate the possibility of variation associated with period of gestation, attention was confined to the 1,970 (of 4,931) children born between 273 and 286 days. Stillbirths and neonatal deaths were excluded. To reduce the

amount of home visiting a sample was selected, consisting of half the infants whose placentae weighed between 20 and 28 ozs, and all infants with placentae above and below these weights. There were 822 children in the sample and heights of both parents of 506 were measured.

BIRTH WEIGHT ACCORDING TO PARENTAL HEIGHT

Birth weight, heights of both parents, birth rank, sex and duration of gestation were available for 1,028 of the 1,243 Smethwick single births alive one month after birth. Table 1 gives mean birth weight according to parental height and shows that birth weight increases regularly as height of mother increases. The association between birth weight and height of father is less marked and less consistent. In view of the correlation between heights of parents (0.20 for parents of the 1,028 children) it seemed desirable to standardise in each case for height of the other parent; the results are also given in table 1 (and fig. 1). The association between birth weight and mother's height is virtually unchanged, but the association between birth weight and father's height is less evident.

The same data are given in table 2 for the 506 Birmingham children alive at one month; the results are also consistent with the conclusion that mean birth weight increases with height of mother, but shows no consistent association with height of father. It should be noted that these data were entirely independent of the Smethwick material from which they differ in three respects: (a) father's height was measured for the purposes of the enquiry, and hence can

TABLE 1. MEAN BIRTH WEIGHT (LB.) ACCORDING TO HEIGHT OF PARENTS (SMETHWICK DATA)

Height of Mothers (Inches)	Height of Fathers (Inches)						Total	Mean Standardized for Height of Father
	Under 64	64–	66–	68–	70–	72 and over		
Under 60	6.28	5.69	6.86	6.58	7.13	7.15	6.61	6.73
	(8)	(4)	(8)	(9)	(6)	(3)	(38)	
60–	6.90	7.12	6.61	7.10	6.81	7.09	6.92	6.91
	(16)	(11)	(24)	(39)	(27)	(12)	(129)	
62–	7.06	7.07	7.21	7.27	7.52	7.52	7.30	7.31
	(17)	(38)	(63)	(63)	(56)	(38)	(275)	
64–	7.37	7.26	7.21	7.40	7.41	7.49	7.34	7.35
	(9)	(47)	(97)	(65)	(84)	(45)	(347)	
66–	7.22	7.75	7.68	7.50	7.26	7.90	7.56	7.55
	(4)	(16)	(40)	(46)	(44)	(27)	(177)	
68 and over	8.41	7.79	7.62	7.81	7.53	7.86	7.70	7.74
	(2)	(3)	(4)	(11)	(28)	(14)	(62)	
Total	7.01	7.21	7.22	7.32	7.35	7.57	7.31	—
	(56)	(119)	(236)	(233)	(245)	(139)	(1028)	
Mean standardized for height of mother	7.22	7.25	7.23	7.34	7.33	7.53	—	—

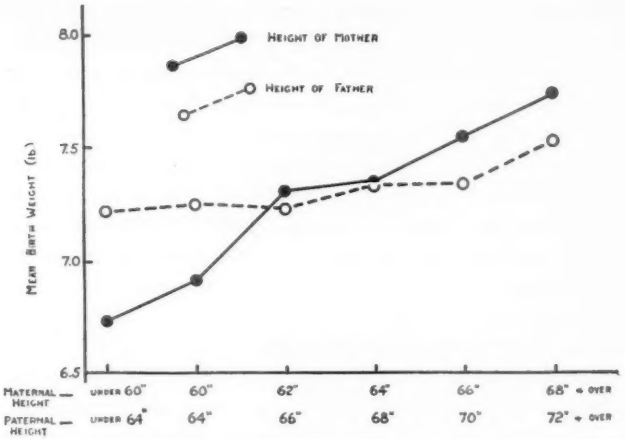

FIG. 1. Birth weight (standardized for height of other parent) according to parental height (Smethwick data).

TABLE 2. MEAN BIRTH WEIGHT (LB.) ACCORDING TO HEIGHT OF PARENTS (BIRMINGHAM DATA)

Height of Mother (Inches)	Under 60	60–	62–	64–	66 and Over
Mean birth weight	6.67	7.28	7.45	7.42	7.59
	(44)	(120)	(154)	(120)	(68)
Mean standardized for height of father	6.62	7.32	7.46	7.41	7.76
Height of Father (Inches)	**Under 66**	**66–**	**68–**	**70–**	**72 and over**
Mean birth weight	7.13	7.46	7.36	7.33	7.66
	(108)	(93)	(134)	(116)	(55)
Mean standardized for height of mother	7.25	7.55	7.33	7.33	7.65

TABLE 3. CORRELATION BETWEEN BIRTH WEIGHT AND PARENTAL HEIGHT

Sex of Infants	Correlation Between Birth Weight and Height of	Smethwick Data				Birmingham Data		
		Total	Corrected for height of other parent	Corrected for gestation and height of other parent	No. of observations and standard error	Total	Corrected for height of other parent	No. of observations and standard error
Males	Mother	0.20	0.18	0.18	545	0.22	0.18	248
	Father	0.10	0.07	0.06	(0.04)	0.13	0.05	(0.06)
Females	Mother	0.21	0.18	0.19	483	0.17	0.15	258
	Father	0.16	0.12	0.10	(0.05)	0.10	0.05	(0.06)
Both sexes	Mother	0.20	0.18	0.18	1028	0.19	0.16	506
	Father	0.13	0.09	0.08	(0.03)	0.11	0.05	(0.04)

be accepted with considerably more confidence; (b) observations are confined to infants born in hospital who are probably weighed somewhat more accurately, and differ slightly in distribution according to parity; and (c) only births delivered between 273 and 286 days gestation are included.

Table 3 gives correlations between birth weight and parental height. For each sex, and for both sets of data, birth weight is more highly correlated with height of mother than with height of father. The same is true of partial correlations, holding constant height of the other parent, for which values (based on both sexes) are respectively 0.18 and 0.09 (Smethwick data) and 0.16 and 0.05 (Birmingham data).

POST-NATAL GROWTH ACCORDING TO PARENTAL HEIGHT

As mentioned above, weights of Smethwick children were recorded at regular intervals during the two years after birth. Weights were accepted only if measured within three weeks of the appropriate date. In exploring the influence of parental height on post-natal growth it was thought desirable to restrict examination to the 625 (of 1,028) children for whom observations at all intervals were available. No adjustment was made for the error introduced by accepting weights obtained at periods up to three weeks before or after the appropriate dates but the effect of this error was examined, and found to be substantial at three months (when weight is still changing rapidly) and trivial at all subsequent intervals. For this reason correlations at 3 months have been excluded.

Table 4 gives correlations at 6, 9, 12, and 24 months between infant weight and parental height, before and after correction for height of other parent. At every interval infant weight is more highly correlated with height of mother than with height of father, and indeed the partial correlations at two years (0.20 and 0.13 respectively for 605 infants) are not very different from those noted at birth (0.18 and 0.09, for 1,028 infants).

TABLE 4. CORRELATION BETWEEN INFANT WEIGHT AND PARENTAL HEIGHT

Sex of Infants	Correlation Between Infant Weight and Heght of:	Age of Infants (Months)								Standard error
		Total	6 Corrected for height of other parent	Total	9 Corrected for height of other parent	Total	12 Corrected for height of other parent	Total	24 Corrected for height of other parent	
Males (328)	Mother	0.22	0.21	0.19	0.19	0.20	0.19	0.20	0.19	0.06
	Father	0.13	0.11	0.12	0.11	0.14	0.12	0.14	0.12	
Females (297)	Mother	0.20	0.18	0.20	0.18	0.21	0.18	0.25	0.22	0.06
	Father	0.10	0.06	0.13	0.10	0.15	0.11	0.18	0.14	
Both sexes (625)	Mother	0.20	0.18	0.19	0.17	0.19	0.18	0.22	0.20	0.04
	Father	0.11	0.09	0.13	0.10	0.14	0.12	0.16	0.13	

TABLE 5. CORRELATION BETWEEN INFANT WEIGHT AND PARENTERAL HEIGHT CORRECTED FOR HEIGHT OF OTHER PARENT, DURATION OF GESTATION, BIRTH RANK AND MATERNAL AGE

Sex of Infants	Correlation Between Infant Weight and Height of	Age of Infants (Months)			
		6	9	12	24
Males	Mother	0.22	0.20	0.21	0.21
	Father	0.12	0.12	0.13	0.13
Females	Mother	0.17	0.17	0.17	0.21
	Father	0.07	0.10	0.11	0.13

Since rate of post-natal growth is affected substantially by duration of gestation and birth rank, and to a lesser extent by maternal age (Cawley, McKeown & Record, 1954) it was thought worthwhile to examine the effect of correction for these variables, as well as for height of the other parent. The results given in table 5 indicate that correlations between infant weight and parental height are only very slightly influenced by these corrections.

DISCUSSION

Investigations of inheritance of size have been concerned mainly with mature animals, and numerous crosses (such as those reported by Punnett & Bailey, 1918; Castle, 1922; Pearse, 1928; Green, 1931; and Livesay, 1930) have provided few data relating size of offspring at birth to the size of their parents. It was the observations of Walton & Hammond (1938) on the Shire-Shetland cross which drew attention to the profound influence which the maternal environment may have on weight at birth, and for a time at least on post-natal development.

The only comparable data of which we are aware are those of Robb on the rabbit (referred to above) which are consistent with the report of Walton & Hammond, and those of Kopec (1924), also on the rabbit, which are not. Kopec crossed Himalayan and Silver breeds, and noted that although birth weight of young from the S♀ × H♂ cross were approximately the same as of young from pure Silver parents (a result in keeping with the Shire-Shetland cross), offspring from the reciprocal H♀ × S♂ cross were intermediate in weight between the two breeds. But having regard to the relatively small differences in birth weight between the pure breeds, numbers of litters examined were small, and it is not certain that account was taken of the influence of parity (since results are based on consecutive matings of the same mothers it is possible that females were mated with males of the same breed before being crossed). Kopec (1922) also mated Himalayan does with both Himalayan and Silver bucks during the same rutting period, and stated that weights of young within the same litter were characteristic of the breed of the male parent. We have not been able to examine the original report of this interesting observation, but substantial numbers would be needed to establish it in view of the con-

siderable variation in weight normally observed among foetuses of the same litter.

In man birth weight is more closely related to height of mother than to height of father. The same association between infant size and the height of the two parents is present in the two years after birth (table 4), and was observed by Paton & Findlay (1926) in children aged 2 weeks to 13 years. They recorded the following correlations (corrected for age of child) between height of children and height of parents:

Mother-son:	0.1585 ± 0.025
Father-son:	0.0767 ± 0.047
Mother-daughter:	0.2829 ± 0.023
Father-daughter:	0.1230 ± 0.044

These discrepancies are apparently eliminated before adult life. They were not observed by Pearson & Lee (1903) who examined correlations between height of parents and height of offspring aged 18 or over, and concluded that "the son and daughter are equally influenced by their father, and equally influenced by their mother".

Mother-son:	0.494
Father-son:	0.514
Mother-daughter:	0.507
Father-daughter:	0.510

Moreover in the Shire-Shetland cross sharp differences between growth rates of hybrid and pure bred foals were established after birth, although the greater influence of the maternal parent was still present at 40 months (the latest period reported). Most other experimental crosses were made by observers interested in the size of mature offspring according to breed of parents, but it seems unlikely that if there had been substantial differences according to sex of parent they would have passed unnoticed.

There is therefore evidence in man and in experimental animals that at birth and for some time after birth size of offspring is related more closely to size of mother than to size of father, but the difference appears to be eliminated before adult life. This result can most reasonably be attributed to the maternal environment, which may have some influence after birth (for example there is a marked difference between the milk supply from Shire and Shetland dams), but is of far greater significance before birth, when the association of infant size with maternal size is established.

The maternal environment may influence size of offspring at birth by an effect on one or both of (a) duration of foetal growth and (b) rate of foetal growth. On the evidence here referred to, the greater association of size of offspring with size of mother than with size of father must be attributed to the influence of the maternal environment on the rate rather than on the duration

of foetal growth. For in man, correction for duration of gestation has virtually no effect on correlations between birth weight and parental height (table 3), and there were only trivial differences between durations of gestation of Shire and Shetland mares. (Although they have no direct bearing on the interpretation of these results, two crosses between animals with different periods of gestation are of interest. Hagedoorn & Hagedoorn (1928) stated that in reciprocal rabbit x hare crosses—a difficult cross to bring about, but one of great interest in view of the substantial difference in length of gestation—duration of gestation was characteristic of the mother. Rife, Gorlaugh, Kunkle, Brandt & Snyder (1943), on the other hand, crossed Aberdeen and Angus breeds of cattle, and noted that the duration of gestation was roughly midway between the periods characteristic of the two breeds.)

Inspection of the results published by Walton & Hammond suggests that the influence of the maternal environment on rate of foetal growth may be determined to some extent by the size of the placenta. Differences between placental weights from the two crosses were as marked as differences in foetal weights, and indeed ratios of foetal to placental weight were very nearly the same. But variation in placental size only partly accounts for variation in rate of foetal growth in relation to litter size (McKeown & Record, 1953a) and birth rank (McKeown & Record, 1953b), and it is quite possible that it does not wholly explain the association between birth weight and mother's size. Moreover by attributing foetal size to placental size we do not greatly advance understanding of the way in which the maternal environment regulates growth, for the placenta is also a foetal structure, and we must then enquire in what way the maternal environment limits the size of the placenta.

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SUMMARY

Association between infant weight and parental stature is examined in two independent series of 1,028 and 506 children. It is shown that at birth, and during two years after birth, infant weight increases with height of mother, but is only slightly affected by height of father. This result is independent of duration of gestation, and it is suggested that it must be attributed to the influence of the maternal environment on rate of foetal growth.

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Influence of Pre-Natal Environment on Correlation between Birth Weight and Parental Height

THOMAS McKEOWN AND R. G. RECORD

Department of Social Medicine, University of Birmingham, England

IT HAS BEEN SHOWN that birth weight is more closely related to height of mother than to height of father (Cawley, McKeown & Record, 1954). Since this result was independent of duration of gestation, it was attributed to the influence of the maternal environment on rate of foetal growth. This influence might be expected to be most conspicuous in circumstances in which foetal growth is most seriously retarded, for example in multiple pregnancies and in first pregnancies. In the present communication we examine correlation between birth weight and parental height according to litter size[1] and birth rank. We also enquire to what extent association between maternal size and rate of foetal growth is related to the size of the placenta.

LITTER SIZE

In man, as in most experimental animals, birth weight is inversely related to size of litter. The low weight of multiple births is due partly to early onset of labour, and partly to retardation of foetal growth during the last weeks of gestation. The time at which retardation appears varies with size of litter, being approximately 26 weeks for quadruplets, 27 weeks for triplets and 30 weeks for twins (McKeown & Record, 1952). In each case retardation is marked (as indicated by comparison with the rate of growth of singletons) and there is therefore good reason to believe that in multiple pregnancy foetal development is seriously restricted by the maternal environment.

Since the provision which the maternal environment makes for foetal growth is determined to some extent by size of mother (as indicated by height) it was thought of interest to compare correlations between birth weight and parental height in single and twin pregnancy. For this purpose we make use of data for 1,028 and 506 singletons previously described (Cawley, McKeown & Record, 1954), and of an independent series of twin births of which an account has also been given (McKeown & Record, 1954). Data included birth weight, parity, sex, duration of gestation, height of both parents and (except in the case of the 1,028 single births) placental weight.

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[1] It is appreciated that the term "litter size" may be considered undesirable when used in reference to the number of human births, but we found no satisfactory alternative.

TABLE 1. MEAN LITTER WEIGHT (LB.) OF TWINS ACCORDING TO HEIGHT OF PARENTS

Height of Mother (Inches)	Under 60	60–	62–	64–	66–	68 and Over
Mean litter weight	10.33	10.83	11.07	11.29	11.54	13.59
	(23)	(73)	(133)	(90)	(38)	(18)
Mean litter weight standardized for height of father	10.01	10.94	11.03	11.24	11.65	13.91
Height of Father (Inches)	**Under 64**	**64–**	**66–**	**68–**	**70–**	**72 and over**
Mean litter weight	10.91	11.26	11.14	11.31	11.08	11.53
	(23)	(54)	(96)	(88)	(84)	(30)
Mean litter weight standardized for height of mother	10.95	11.23	11.31	11.25	11.01	11.34

In examination of birth weight it is of course necessary to use the combined weight of the twin pair. Table 1 gives mean litter weight according to parental height, and shows that as in single pregnancy weight increases sharply with mother's height, but is apparently unrelated to father's height. In view of the correlation between parents' heights, it has been thought desirable to correct for height of other parent. This adjustment has been made by standardisation, and has no substantial effect on the result.

That association between birth weight and parental height is sharper in twin pregnancy than in single pregnancy is suggested by the correlations given in Table 2. After correction for height of other parent, correlation in twin pregnancy between birth weight and mother's height (0.24) is higher, and correlation between birth weight and father's height (−0.02) is lower, than in single pregnancy. Indeed father's height appears to have no influence on birth weight of twins.

It was shown previously that in single pregnancy association between birth weight and mother's height is independent of length of gestation. This is also the case in twin pregnancy (although there is a substantial positive correla-

TABLE 2. CORRELATIONS BETWEEN BIRTH WEIGHT AND PARENTAL HEIGHT ACCORDING TO LITTER SIZE

	Number of Pregnancies	Correlation Between Foetal Weight and:				Standard Error
		Mother's height	Father's height	Mother's height (Corrected for height of other parent)	(Father's height (Corrected for height of other parent)	
Twins	375	0.25	0.05	0.24	−0.02	0.05
Singletons						
Smethwick data	1,028	0.20	0.13	0.18	0.09	0.03
Birmingham data	506	0.19	0.11	0.16	0.05	0.04

tion between length of gestation of twins and mother's height, McKeown & Record, 1954). The relevant correlations are as follows:

	Birth Weight and Mother's Height	Birth Weight and Father's Height
Corrected for gestation	0.25	0.06
Corrected for gestation and height of other parent	0.24	−0.01

It is concluded that in twin, as in single pregnancy, association between birth weight and mother's height is determined by the influence of maternal size on rate of foetal growth.

BIRTH RANK

It is well known that birth weight increases with birth rank. This association must be attributed to variation in rate of foetal growth, for there is a small negative correlation between length of gestation and birth order (Karn & Penrose, 1951). There is no evidence of a difference between growth rates of first and later born until about 36–37 weeks, but from this time later born are heavier than first born (McKeown & Record, 1953 b).

In view of this result it was anticipated that correlation between birth weight and maternal height would be sharper in first than in later pregnancies, although the difference might be less conspicuous than that associated with litter size, since retardation of foetal growth is much less marked in first pregnancies than in multiple pregnancies. Table 3 gives data based on the two series of single births. In both, after correction for height of other parent, the difference between correlations of birth weight with height of mother and height of father is greater in first born than in later born; but the errors of the correlations are substantial, and the evidence is suggestive rather than conclusive. Two sets of data have therefore been combined, and mean weights calculated according to parental height; adjustments have again been introduced for height of other parent. The results are illustrated in Fig. 1, in which the points represent mean standardized birth weights, and the straight lines represent partial regression of weight on parental height. The data suggest that mean birth weight is more

TABLE 3. CORRELATION BETWEEN BIRTH WEIGHT AND PARENTAL HEIGHT ACCORDING TO BIRTH RANK

Birth Rank	Smethwick Data				Birmingham Data			
	Number	Correlations, corrected for height of other parent, between foetal weight and:		Standard error	Number	Correlations, corrected for height of other parent, between foetal weight and:		Standard error
		Mother's height	Father's height			Mother's height	Father's height	
First born	416	0.22	0.13	0.05	222	0.31	−0.03	0.07
Later born	612	0.14	0.09	0.04	284	0.09	0.10	0.06

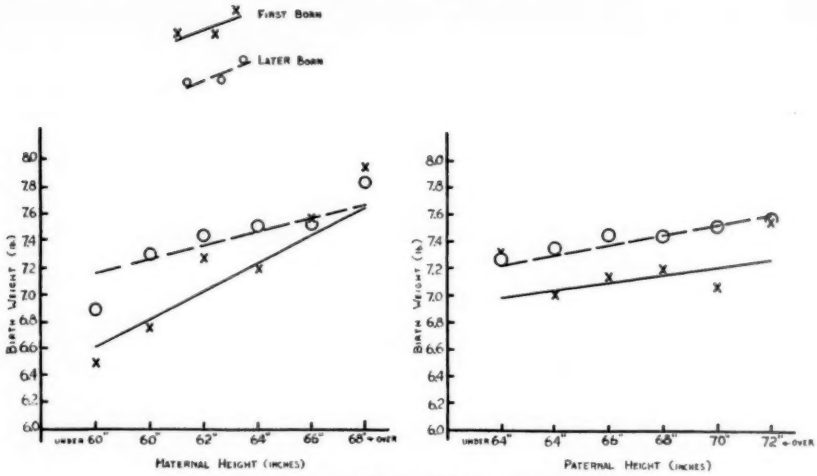

FIG. 1. Regression of birth weight on parental weight

sharply related to height of mother in first than in later pregnancies. Since there is only a trivial correlation between length of gestation and maternal height in single pregnancy, this result must be attributed to the fact that the influence of maternal size on rate of foetal growth is more marked in first born than in later born.

There is also a difference between growth rates of male and female foetuses (from 30–31 weeks gestation: McKeown & Record, 1953 b) and it was thought of interest to examine correlation between birth weight and parental height according to sex. Results (Table 4) based on the two series of single births are inconclusive, which is scarcely surprising in view of the small difference between growth rates of male and female foetuses.

THE INFLUENCE OF PLACENTAL SIZE ON CORRELATION BETWEEN BIRTH WEIGHT AND PARENTAL HEIGHT

In the Shire-Shetland cross reported by Walton & Hammond (1938) weight of placenta was closely related to weight of foetus, and indeed the proportion

TABLE 4. CORRELATION BETWEEN BIRTH WEIGHT AND PARENTAL HEIGHT ACCORDING TO SEX

Sex	Smethwick Data				Birmingham Data			
	Number	Correlations, corrected for height of other parent, between foetal weight and:		Standard error	Number	Correlations, corrected for height of other parent, between foetal weight and:		Standard error
		Mother's height	Father's height			Mother's height	Father's height	
Males	545	0.18	0.07	0.04	248	0.18	0.05	0.06
Females	483	0.18	0.12	0.05	258	0.15	0.05	0.06

of combined foetal and placental weight represented by placental weight was approximately the same for hybrids and pure breeds. This suggested that variation in foetal weight according to maternal size might be accounted for by variation in placental size, in which case it would be necessary to enquire in what way the maternal environment limits growth of the placenta.

But in man although foetal and placental weights are fairly highly correlated (Calkins, 1937, gives an estimate of 0.56) the influence of the maternal environment on rate of foetal growth is not wholly determined by placental size. For example a substantial difference between growth rates of singletons and twins remains when allowance is made for the difference in placental weight (McKeown & Record, 1953 a), and the difference in weights of first and later born is not entirely explained by the fact that the placenta is larger for later born than for first born (McKeown & Record, 1953 b).

Placental weights were available for 506 Birmingham single births, and for 375 pairs of twins; correlations between foetal and placental weights for the two series were 0.65 and 0.56 respectively. Table 5 shows the effect of correction for placental weight on correlations between birth weight and parental heights. For both singletons and twins, placental weight is correlated with parental height, and is more highly correlated with height of mother than with height of father. But fixing placental weight has little effect on correlation between foetal weight and parental height, whereas fixing foetal weight almost eliminates correlation between placental weight and parental height.

It is concluded that the influence of the maternal environment on rate of foetal growth according to size of mother is not determined mainly by an influence on the size of the placenta. The data given in Table 6 are consistent with the same conclusion in respect of the differences noted in Table 3 in relation to birth order. Placental weights were available for 222 first born and 284 later

TABLE 5. THE INFLUENCE OF PLACENTAL WEIGHT ON CORRELATION BETWEEN FOETAL WEIGHT AND PARENTAL HEIGHT

	Correlation Between:			
	Foetal weight and		Placental weight and	
	Mother's height	Father's height	Mother's height	Father's height
Singletons (506)	0.19	0.11	0.13	0.10
Corrected for:				
Height of other parent	0.16	0.05	0.10	0.06
Height of other parent and placental weight	0.13	0.02	—	—
Height of other parent and foetal weight	—	—	0.00	0.03
Twins (375)	0.25	0.05	0.18	0.07
Corrected for:				
Height of other parent	0.24	−0.02	0.16	0.02
Height of other parent and placental weight	0.19	−0.04	—	—
Height of other parent and foetal weight	—	—	0.03	0.04

TABLE 6. THE INFLUENCE OF PLACENTAL WEIGHT ON CORRELATION BETWEEN FOETAL WEIGHT AND PARENTAL HEIGHT. (SINGLETONS ONLY)

Birth Rank	Correlation Between:			
	Foetal weight and		Placental weight and	
	Mother's height	Father's height	Mother's height	Father's height
First born (222)	0.32	0.07	0.22	0.04
Corrected for:				
Height of other parent	0.31	−0.03	0.22	−0.04
Height of other parent and placental weight	0.23	−0.01	—	—
Height of other parent and foetal weight	—	—	0.05	−0.02
Later born (284)	0.13	0.14	0.09	0.15
Corrected for:				
Height of other parent	0.09	0.10	0.05	0.13
Height of other parent and placental weight	0.08	0.03	—	—
Height of other parent and foetal weight	—	—	−0.02	0.07

born, for which correlations between foetus and placenta were respectively 0.60 and 0.68. Correlations between foetal weight and parental height are again not much affected by fixing placental weight, but correlations between placental weight and parental height are substantially reduced by fixing foetal weight. Numbers are of course small, and the results are no more than suggestive.

SUMMARY

Data recorded for two series of 1,028 and 506 singletons, and for 375 pairs of twins, are used to explore the influence of litter size and birth rank on association between birth weight and parental height. In twin pregnancy, after correction for height of other parent, correlation between birth weight and mother's height (0.24) is higher, and correlation between birth weight and father's height (−0.02) is lower, than in single pregnancy. Similarly, in single pregnancy, association between birth weight and parental height is more marked for first than for later born. These results are independent of duration of gestation, and are attributed to the influence of the maternal environment on rate of foetal growth.

For both singletons and twins, placental weight is more highly correlated with height of mother than with height of father. But correction for placental weight has little effect on correlation between foetal weight and parental height, whereas correction for foetal weight almost eliminates correlation between placental weight and parental height. It is concluded that the influence of the maternal environment on rate of foetal growth according to size of mother is not determined mainly by an influence on the size of the placenta.

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BOOK REVIEWS

General Virology

By S. E. Luria (Professor of Bacteriology, University of Illinois). 427 + xiv Pp. John Wiley and Sons, Inc., New York, 1953. $8.50.

DR. LURIA'S remarkably up-to-date book is a "general virology" not only by virtue of its equal preoccupation with viruses of bacterial, plant and animal hosts, and its emphasis on the intertwining of virus infection with cell biology, but also by the exclusion of most special information about individual viruses and the diseases they cause. Just enough detail is given to exemplify the general principles of each chapter. Most of the experiments are quoted from bacteriophage lore, but the author has deliberately tried to incorporate as much as possible of research on other viruses.

The author has played a central role in modern virological research and this is likely to remain the definitive text of its kind. The logical structure and the detailed content (excepting some rare, perhaps inevitable, lapses of speculation on work too recent for mature judgment) are impeccable.

A reviewer is often expected to seek out at least one feature to criticize. The worst I can find is a rhetorical weakness,—the topical organization is followed so consistently that the subject matter tends to be categorized in dispersed sets of supporting facts to justify each principle; the reader is rarely stimulated by an anecdotal account.

Human geneticists seeking information on medical aspects of virus diseases would be misdirected, but all biologists may look to this book for the new facts of viral life.

J. LEDERBERG
University of Wisconsin

A Genetic and Neuropsychiatric Investigation of a North-Swedish Population

By J. A. Böök (State Institute for Human Genetics, Uppsala, Sweden). Printed by S. Karger, Basel; available from State Institute for Human Genetics, Uppsala. 1953. Pp. 177. $6.00.

THIS MONOGRAPH consists of reprints of three papers which appeared originally in *Acta Genetica et Statistica Medica* (4: 1–100; 133–139; 345–414) and which have now been bound together without change in pagination.

A very interesting study is presented of the major neuropsychiatric disorders encountered in an isolated population in Sweden. The investigation area consisted of three parishes in the extreme north, within the Arctic Circle and bordering Finland. The 1949 population of the area was 8,981, predominantly descendants of persons who migrated into the area between 1650 and 1730. The area is rural, and the population has a low migration rate, a high fertility rate, and a first cousin marriage rate estimated at 2.2 per cent. The general character of the area and its population thus conform to the concept of an isolate as this term is used in population genetics.

By means of a study of parish registers, hospital and other medical reports and personal visits, an attempt was made to ascertain all individuals with major neuropsychiatric dis-

orders who were living on September 1, 1949. The population yielded 85 index cases of schizophrenia, 2 of manic-depressive psychosis, 4 with involutional psychoses, 21 patients with convulsive disorders and 72 with oligophrenia of all types. The families of these propositi were studied and secondary cases investigated. Morbid risk figures for relatives of the index cases and for the entire population are calculated.

The empiric risk figures that are estimated for relatives of the index cases and for the total population of the isolate are of considerable interest. For example, the risk figures for relatives of schizophrenic index cases agree well with those found in other studies. However, the general morbidity risk of schizophrenia in this population is estimated to be about three times as great as that found in other North European and American populations. This relationship between family and population risk figures is cited as additional evidence in favor of the genetic hypothesis of the etiology of schizophrenia. The findings suggest a high frequency of the responsible gene in this population as a result of isolation and genetic drift, perhaps aided and abetted by an unusually high rate of reproductive fitness (estimated at 70 per cent) of the affected individuals in this population. In contrast, manic-depressive psychosis has a very low incidence in the isolate, suggesting genetic drift in the opposite direction with respect to this gene. Among the oligophrenics an unusual clinical entity designated "genetic spastic oligophrenia" was found in 24 patients, apparently due to a simple recessive gene. All but one of the 16 sibships containing affected persons were related by blood and could be put on one pedigree.

In the reviewer's opinion the chief value of this monograph lies in its description of a population isolate and in its comparisons with the general Swedish population. Many more studies of this sort are needed to provide data for better understanding of population dynamics in man. As the author himself points out, some of the interpretations suggested should be viewed with considerable reserve, as the calculations are based on very small numbers and on certain assumptions which may or may not be correct. In particular, this reviewer would suggest caution with regard to the interpretation of the genetic mechanism in schizophrenia and the estimate of an unusually high mutation rate for this condition. The methods followed in arriving at some of the estimates are of considerable methodologic interest. In general, this monograph is recommended to anyone interested in population genetics.

C. NASH HERNDON
Bowman Gray School of Medicine

REPORT OF THE SECRETARY

A. MEMBERSHIP AND SUBSCRIBERS TO THE JOURNAL

This is my last report as secretary and it is time for a change. In the previous report 170 new nominations or subscriptions were recorded, but this time there are only 86. The new secretary, D. C. Rife, has an ambitious membership program already started and it is assumed that each member will not only help, if called upon, but will also take the initiative and find a new member, whom he will nominate, sending the information to Professor Rife, at the Ohio State University.

The strength of the Society as of September 1, 1954, follows:

Patrons	3
Life Members	3
Active Members	475
Associate Members	23
Corresponding Members	61
Individual, non-member subscriptions	23
Institutional subscriptions	
Foreign	88
Domestic	228
Total	904

The fact that there are less than 50 members and institutions now suspended for lack of payment of their 1954 obligations, is a tribute to the persistence and diplomacy with which the treasurer, Nash Herndon, has kept after the dilatory ones.

B. NOMINATIONS AND ELECTIONS

The nominating committee was composed of C. P. Oliver, T. Dobzhansky and Gordon Allen. The following persons were elected for duty:

For one year terms

President	C. N. Herndon, M.D.
Vice President	Harold Cummins
President-elect	S. C. Reed

For two year terms

Directors at large—Howard Levene
—C. C. Li
—N. F. Walker

For three year terms

Secretary	D. C. Rife
Treasurer	W. E. Heston

C. APPOINTMENTS

The Board of Directors accepted the resignation of H. H. Strandskov as editor and voted their appreciation of the services he has provided the Society. Dean L. H. Snyder of the

University of Oklahoma was appointed editor and the following members were appointed as associated editors:

For one year terms

Ray C. Anderson, M.D.
Paul David

For two year terms

Philip Levine, M.D.
William J. Schull

For three year terms

Horace W. Norton
James N. Spuhler

It is assumed that all members will be willing to read any papers sent them for criticism by our new editor.

D. THE GAINESVILLE MEETINGS

There was a very good attendance, when one remembers that a meeting scheduled in one of the less heavily populated corners of the country cannot expect a very large turnout. For those who did get to Florida, the experience was an unusually pleasant and profitable one. Local arrangements were managed expertly by A. M. Winchester.

The weather was clear and hot from September 5–9, 1954. However, the meetings were held in air conditioned rooms as was the annual dinner. The presidential address, by J. V. Neel, M.D., was stimulating and very much appreciated by the 83 persons who heard it.

The meetings next September will be at East Lansing, Michigan. As this is more centrally located, a much larger attendance is expected.

Respectfully submitted,
SHELDON C. REED
Secretary

BIBLIOGRAPHY OF HUMAN GENETICS

Prepared by
Dr. V. RAE PHELPS
P. O. Box 522, East Lansing, Michigan

THIS SECTION is a continued list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made and is being made to make the list both up to date and complete, but to do so is a difficult task. Everyone who finds the list useful and considers a complete one desirable, can be of help by sending to the bibliographic editor, at the address given above, any recent reference which has been missed or references to papers in press. The bibliographic editor wishes to take this opportunity to thank the many people who have been and it is hoped, will continue to be of help in this way.

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PATRONS

W. P. DRAPER
322 East 57th Street
New York, New York

C. M. GOETHE
Anglo Bank Building
Sacramento 14, California

A. S. WIENER, M.D.
64 Rutland Road
Brooklyn 25, New York

LIFE MEMBERS

CHARLES W. COTTERMAN
Wadley Research Institute
3600 Gaston Avenue
Dallas 4, Texas

RICHARD H. POST
Quogue, Long Island
New York

DEAN L. H. SNYDER
The Graduate School
University of Oklahoma
Norman, Oklahoma

ROBERT M. STECHER, M.D.
City Hospital
3395 Scranton Road
Cleveland 9, Ohio

HERLUF H. STRANDSKOV
Dept. of Zoology
The University of Chicago
Chicago 37, Illinois

ACTIVE MEMBERS

DAVID ADLERSBERG, M.D.
136 East 64th Street
New York 21, New York

LEO ALEXANDER, M.D.
433 Marlborough St.
Boston 15, Mass.

FRED H. ALLEN, JR., M.D.
300 Longwood Avenue
Boston 15, Massachusetts

GORDON ALLEN, M.D.
112 Second Ave.
Pelham 65, New York

J. G. ALLEN
John Carroll University
Biology Department
Cleveland 18, Ohio

WALTER C. ALVAREZ, M.D.
700 N. Michigan Avenue
Chicago, Illinois

E. H. Amidon (Mrs.)
Box 166
Town of Central Square, New York

Dorothy H. Andersen, M.D.
Babies Hospital
167th St. and Broadway
New York City, New York

Ray C. Anderson, M.D.
The Dight Institute
University of Minnesota
Minneapolis 14, Minnesota

V. Elving Anderson
The Dight Institute
University of Minnesota
Minneapolis 14, Minnesota

J. Lawrence Angel
Daniel Bough Institute of Anatomy
Jefferson Medical College
307 South 11th Street
Philadelphia 7, Pennsylvania

T. S. Argyris
Department of Anatomy
Harvard Medical School
Boston 15, Mass.

Frieda W. Arkin
27 West 96th St.
New York, N. Y.

Bertha M. Aschner, M.D.
3 East 74th Street
New York 21, New York

Richard Ashman
5902 Marshal Foch Street
New Orleans 24, Louisiana

Mary L. Austin
Dept. of Zoology
Wellesley College
Wellesley, Mass.

R. L. Baer, M.D.
962 Park Avenue
New York City, New York

Harry Bakwin, M.D.
132 East 71st Street
New York 21, N. Y.

Ruth M. Bakwin, M.D.
132 East 71st Street
New York 21, New York

Bert Ballin, D.D.S.
94 Prospect Street
Stamford, Connecticut

Ivan J. Barber, Jr.
Dept. of Anatomy
University of Texas,
Medical Branch
Galveston, Texas

Natalie Barish
Department of Zoology & Entomology
Ohio State University
Columbus, Ohio

G. R. Barrett
Holstein-Friesian Association of America
Brattleboro, Vermont

Florence L. Barrows
76 Elm Street
Northampton, Mass.

Elizabeth Barto
Laboratory of Vertebrate Biology
1135 E. Catherine Street
Ann Arbor, Michigan

Helen I. Battle
Department of Zoology
University of Western Ontario
London, Ontario, Canada

Julius Bauer, M.D.
1680 Vine Street
Los Angeles 28, California

Nathan Beckenstein, M.D.
681 Clarkson Avenue
Brooklyn 3, New York

Lauretta Bender, M.D.
Department of Psychiatry
New York University College of Medicine
477 First Avenue
New York 16, New York

J. L. Bennett, M.D.
Creedmoor State Hospital
80-45 Winchester Blvd.
Queens Village 27, N. Y.

Samuel G. Berkow, M.D.
Hobart Professional Building
Perth Amboy, New Jersey

J. B. Birdsell
Department of Anthropology
University of California
Los Angeles 25, California

Auray Blain
Montreal Botanical Gardens
4101 Sherbrooke St., East
Montreal, P.Q.
Canada

A. P. BLAIR
Department of Zoology
University of Tulsa
Tulsa 4, Oklahoma

A. F. BLAKESLEE
Smith College
Genetics Experiment Station
Northampton, Massachusetts

DUNCAN BLEWETT, M.D.
106 S. Goodwin St.
Urbana, Illinois

HARRY BLOCH, M.D.
1745 President Street
Brooklyn 13, New York

DAVID BLOOM, M.D.
135 E. 50th Street
New York 22, New York

WILLIAM C. BOYD, M.D.
Dept. of Immunochemistry
Boston University Medical School
80 E. Concord St.
Boston, Massachusetts

MABEL G. BOYDEN
Rutgers University
New Brunswick, New Jersey

G. J. BRANCATO, M.D.
449 Bay Ridge Parkway
Brooklyn 9, New York

MARY F. BREW, M.D.
145 Avondale Place
Syracuse 10, New York

O. L. BRIDGMAN, M.D.
323 Barbara Way
Hillsborough, California

JEAN BRIERLEY
Biol. Science Department
Michigan State College
East Lansing, Michigan

WALTER H. BROSHAR, SR.
2332 Noble St.
Anderson, Indiana

KENETH S. BROWN
5555 South Kenwood
Chicago 37, Illinois

B. C. BROWNSON, M.D.
San Mateo Clinic
San Mateo, California

ALICE M. BRUES
University of Oklahoma School of Medicine
801 N. E. 13th Street
Oklahoma City, Oklahoma

WM. A. BRUMFIELD, JR., M.D.
College of Medicine
N. Y. State University
Syracuse, N. Y.

VIRGINIA F. BRUNO (MRS.)
26314 Belle Porte Avenue
Harbor City, California

ADELAIDE K. BULLEN
Florida State Museum
Gainesville, Florida

FRANZ BUSCHKE, M.D.
1211 Marion Street
Seattle 4, Washington

A. J. BUTLER
The Training School
Vineland, New Jersey

WILLIAM S. BUTTS, M.D.
909 Kamiaken Street
Pullman, Washington

HENRY M. BUTZEL, JR.
Biology Department
Union College
Schenectady, New York

D. EWEN CAMERON, M.D.
1025 Pine Avenue West
Montreal 2, Canada

P. B. CANDELA, M.D.
Box 549, Main P.O.
Los Angeles, California

J. FLOYD CANNON
Salt Lake Clinic
115 East on South Temple
Salt Lake City 1, Utah

A. J. CARLSON
Department of Physiology
University of Chicago
Chicago, Illinois

GWENYTH LESLIE CARSON
972 Euclid Avenue
Berkeley, California

G. L. CARVER
Dept. of Biology
Mercer University
Macon, Georgia

R. B. CATTELL
106 S. Goodwin Street
Urbana, Illinois

ROBERT CAUSBIE
177 Inca Street
Denver, Colorado

C. C. CHAPPLE, M.D.
1740 Bainbridge Street
Philadelphia 46, Pennsylvania

H. B. CHASE
Department of Biology
Brown University
Providence 12, Rhode Island

A. M. CHICKERING
Albion College
Albion, Michigan

BARTON CHILDS, M.D.
The Johns Hopkins Hospital
Baltimore 5, Maryland

ANTONIO CIOCCO
School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania

E. A. CLAAR (MRS.)
617 Thornwood Lane
Northfield, Illinois

C. W. CLANCY
Department of Biology
University of Oregon
Eugene, Oregon

PHILIP J. CLARK
Institute of Human Biology
University of Michigan
Ann Arbor, Michigan

A. C. CLEMENT
Department of Biology
Emory University
Emory University, Georgia

BERNICE H. COHEN (MRS.)
3402 Devonshire Drive
Baltimore 15, Maryland

MANDEL E. COHEN, M.D.
Massachusetts General Hospital
Boston, Massachusetts

E. C. COLIN
Chicago Teachers College
6567 Harvard Avenue
Chicago 21, Illinois

ALFRED T. COLLETTE
209 Lyman Hall
Syracuse University
Syracuse 10, N. Y.

DONALD C. COLLINS, M.D.
Suite 503
7046 Hollywood Blvd.
Hollywood 28, California

ROBERT C. COOK
American Genetics Association
1507 M Street, N. W.
Washington 5, D. C.

JAMES F. CROW
Genetics Department
University of Wisconsin
Madison, Wisconsin

FRANK W. CROWE, M.D.
209 Main Street
Boise, Idaho

HAROLD CUMMINS
Department of Anatomy
Tulane University
New Orleans 18, Louisiana

J. H. CURRENS, M.D.
Massachusetts General Hospital
Boston 14, Mass.

HELEN O. CURTH, M.D.
35 East 84th Street
New York 28, N. Y.

D. D. CURTIS
13 Benson Ave.
Peterborough, Ont.
Canada

A. A. DAHLBERG, D.D.S.
5756 Harper Avenue
Chicago 37, Illinois

H. L. DAIELL, M.D.
4250 N. Larkin
Milwaukee 11, Wisconsin

J. J. DANEK, M.D.
2767 80th Avenue
New Hyde Park, L. I.
New York

C. H. DANFORTH
Department of Anatomy
Stanford University
Stanford, California

JULIUS W. DAVENPORT, JR., M.D.
7011 Broad Place
New Orleans 25
Louisiana

PAUL R. DAVID
Department of Zoological Sciences
University of Oklahoma
Norman, Oklahoma

I. DAVIDSOHN, M.D.
Mount Sinai Hospital
2750 W. 15th Place
Chicago 8, Illinois

RICHARD DAY, M.D.
Dept. of Pediatrics
College of Medicine
451 Clarkson Avenue
Brooklyn 3, N. Y.

DONALD DELAHAYE, M.D.
Department of Pathology
Hospital for Sick Children
Toronto, Ontario, Canada

F. DEMARINIS
Fenn College
Cleveland, Ohio

E. R. DEMPSTER
314 Hilgard Hall
University of California
Berkeley 14, California

EDWARD DENGROVE, M.D.
314 Crassmere Ave., Interlaken
Asbury Park, New Jersey

KENNETH E. DERIFIELD
Arizona State Teachers College
Flagstaff, Arizona

LEWIS A. DEXTER
213 Elm Street
Chevy Chase 15, Maryland

LEE R. DICE
Institute of Human Biology
1135 E. Catherine
Ann Arbor, Michigan

WILLARD M. DILLON
Department of Dairy Science
College of Agriculture
University of Illinois
Champaign, Illinois

TH. DOBZHANSKY
Schermerhorn Hall
Columbia University
New York 27, N. Y.

DAVID A. DOLOWITZ, M.D.
912 East First Street
Salt Lake City 2, Utah

HAROLD F. DORN
15 Burning Tree Court
Bethesda 14, Maryland

L. C. DUNN
Department of Zoology
Columbia University
New York 27, New York

PAUL F. DWAN, M.D.
Variety Club Heart Hospital
University of Minnesota
Minneapolis 14, Minnesota

R. W. EHRICH
Department of Soc.-Anthropology
Brooklyn College
Brooklyn 10, New York

JOHN ELLIOTT, M.D.
Director, Blood Bank of Dade County, Inc.
1800 N. W. Tenth Avenue
Miami 36, Florida

F. E. EMERY
Medical School
Little Rock, Arkansas

MILTON ENDE, M.D.
8 Marshall Street
Petersburg, Virginia

W. G. ERWIN
Department of Biological Science
Northwestern State College
Natchitoches, Louisiana

ARTHUR FALEK
74-37 43rd Avenue
Elmhurst, New York

HAROLD F. FALLS, M.D.
University Hospital
Ann Arbor, Michigan

G. FANKHAUSER
Department of Biology
Princeton University
Princeton, New Jersey

LISSY FEINGOLD
310 W. 72nd St.
New York 23, N. Y.

PAUL FEJOS
The Wenner-Gren Foundation
14 East 71st Street
New York 21, New York

A. FERRARO, M.D.
150 East 93rd Street
New York, New York

M. T. FLIEGELMAN, M.D.
1708 Hayburn Bldg.
Louisville 2, Kentucky

SEYMOUR FOGEL
Brooklyn College
Department of Biology
Flatbush and Avenue H
Brooklyn 10, New York

CLELLAN S. FORD
205 Whitney Avenue
New Haven, Connecticut

MORRIS FOSTER
Osborn Zoological Laboratory
Yale University
New Haven 11, Connecticut

F. C. FRASER, M.D.
Department of Genetics
McGill University
Montreal, Canada

CHESTER N. FRAZIER, M.D.
Massachusetts General Hospital
Boston 14, Massachusetts

MAX W. FRIEDMANN, M.D.
251 Central Park West
New York 24, New York

H. W. FRINGS
Department of Zoology
Pennsylvania State College
State College, Pennsylvania

JOHN A. FRISCH, S. J.
Canisius College
Buffalo 8, New York

JOHN GARB, M.D.
219 East 19th Street
New York 3, New York

ELDON J. GARDNER
Department of Zoology
Utah State Agricultural College
Logan, Utah

STANLEY M. GARTLER
21 Chittenden Avenue
New York 33, New York

L. E. GAUL, M.D.
509 Hulman Bldg.
Evansville 8, Ind.

JAMES A. GAVAN
Dept. of Anatomy
South Carolina Medical College
Charleston, S. C.

BENJAMIN R. GENDELL, M.D.
Kennedy Veterans Hospital
Memphis 15, Tennessee

W. C. GEORGE
Medical School
University of North Carolina
Chapel Hill, North Carolina

NATALIE F. GIBBEL
1234 Pacific Street
Brooklyn 16, New York

COLIN GIBSON (MRS.)
64 Castle Frank Crescent
Toronto, Ontario

PHILIP GILBERT
Certified Blood Donor Service
146-16 Hillside Avenue
Jamaica 35, New York

LESTER O. GILMORE
Department of Dairy Science
Ohio Agricultural Experiment Station
Wooster, Ohio

BENSON E. GINSBURG
Whitman Laboratory
University of Chicago
Chicago 37, Illinois

ARTHUR W. GLASS
Department of Biology
Gustavus Adolphus College
St. Peter, Minnesota

H. BENTLEY GLASS
Department of Biology
The Johns Hopkins University
Baltimore 18, Maryland

C. W. GOFF, M.D.
30 Farmington Avenue
Hartford 5, Connecticut

LESTER GOLDMAN, M.D.
53 Leslie Street
Newark 8, New Jersey

H. O. GOODMAN
Dept. of Zoology
Michigan State College
East Lansing, Michigan

EVE B. GORDON (MISS)
62 Leroy Street
New York, New York

MANUEL J. GORDON
2515 Regent Street
Berkeley 4, California

WERNER K. GOTTSTEIN, M. D.
2376 E. 71st St.
Chicago 49, Ill.

JOHN W. GOWEN
Genetics Department
Iowa State College
Ames, Iowa

JOHN B. GRAHAM, M.D.
Box 1020, Medical School
Chapel Hill, N. C.

DOUGLAS GRAHN
Division of Biological Research
Argonne National Laboratory
P. O. Box 299
Lemont, Illinois

P. DONALD GRANT
533 Rockland Avenue
Outremont, Quebec
Canada

MARTHA J. GRAY (MISS)
Higginsville
Missouri

JAMES J. GRIFFITTS, M.D.
Blood Bank of Dade County
1800 N.W. Tenth Avenue
Miami 36, Florida

G. M. GUEST, M.D.
Children's Hospital
Cincinnati, Ohio

H. G. GUILD, M.D.
Johns Hopkins Hospital
Baltimore 5, Maryland

MICHAEL F. GUYER
Biology Building
University of Wisconsin
Madison 6, Wisconsin

S. HABERMAN
Baylor University Hospital
The Graduate Research Institute
Dallas, Texas

EMANUEL HACKEL
Department of Biological Science
Michigan State College
East Lansing, Michigan

D. J. HAGER
Department of Economics
Princeton University
Princeton, New Jersey

GEORGE W. HAGY
Department of Anatomy
Southwestern Medical School
Dallas, Texas

HELENA B. HALE, M.D.
Provincial Hospital
St. John, New Brunswick

A. R. HALE
Department of Anatomy
Tulane University
New Orleans 18, La.

S. L. HALPERIN
45-311 Paliiki Place
Kaneohe, Oahu, T. H.

D. D. HAMMOND
Hunter College
695 Park Avenue
New York 21, New York

SHIRLEY W. HANDLER (MISS)
203 East Crockett
Marshall, Texas

FRANK H. HANKINS
197 Elm Street
Northampton, Massachusetts

BERTRAM L. HANNA
Medical College of Virginia
Richmond 19
Virginia

A. M. HANNAH
Department of Zoology
University of California
Berkeley 4, California

GARRETT HARDIN
399 Arboleda Road
Hope Ranch
Santa Barbara, California

H. M. HARDY (MRS.)
141 Dunvegan Road
Toronto, Ontario, Canada

EMIL M. HARTL
27 Wheeler Street
Boston, Massachusetts

GEORGE W. HARVEY
Scripps Institution of Oceanography
La Jolla, California

CARYL P. HASKINS
Haskins Laboratories
305 East 43rd Street
New York 17, New York

MARGARET E. HATTON, D.D.S.
Orthodontic Research Clinic
Burlington, Ontario
Canada

R. A. HEFNER
Department of Zoology
Miami University
Oxford, Ohio

A. A. HEIDE
1254 N. Springfield Avenue
Chicago 51, Illinoia

GERTRUDE HEIDENTHAL
Russell Sage College
Troy, New York

ELSIE HELSEL
290 E. Dunedin Road
Columbus, Ohio

PAUL S. HENSHAW
17th Floor
501 Madison Avenue
New York, New York

C. N. HERNDON, M.D.
Department of Medical Genetics
Bowman Gray School of Medicine
Winston-Salem 7, North Carolina

EDGAR T. HERRMANN
1365 Lowry Medical Arts Bldg.
St. Paul 2, Minnesota

A. H. HERSH
Department of Biology
Western Reserve University
Cleveland 6, Ohio

IRWIN H. HERSKOWITZ
113 Science Hall
Indiana University
Bloomington, Indiana

MELVIN HERSHKOWITZ
49 West 12th Street
New York 11, N. Y.

W. E. HESTON
National Cancer Institute
Bethesda 14, Maryland

JOSEPH HICHAR
444 Grant Street
Allentown, Pennsylvania

J. M. HILL, M.D.
6752 Avalon Avenue
Dallas 14, Texas

E. A. HINES, M.D.
1331 7th Street, S.W.
Rochester, Minnesota

TAYLOR HINTON
Department of Zoology
University of California
Los Angeles 24, California

PAUL H. HOCH, M.D.
1165 Park Avenue
New York City, New York

GENEVERE F. HOFFMAN (MRS.)
148-25 89th Avenue
Jamaica 2, New York

ALEXANDER HOLLAENDER
Biology Division
Oak Ridge National Laboratory
P. O. Box P
Oak Ridge, Tennessee

S. J. HOLMES
2821 Regent Street
Berkeley 5, California

W. A. HORWITZ, M.D.
722 West 168th Street
New York 32, New York

W. W. HOWELLS
Peabody Museum
Harvard University
Cambridge 38, Mass.

W. E. HOY
Department of Biology
University of South Carolina
Columbia 1, South Carolina

R. R. HUESTIS
Department of Biology
University of Oregon
Eugene, Oregon

ESTELLA M. HUGHES (MRS.)
2019 Fitch Avenue
Kalamazoo 40, Michigan

R. R. HUMPHREY
School of Medicine
University of Buffalo
3435 Main Street
Buffalo 14, New York

TRYPHENA HUMPHREY, M.D.
School of Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

H. R. HUNT
Department of Zoology
Michigan State College
East Lansing, Michigan

L. HUSTED
Miller School of Biology
University of Virginia
Charlottesville, Virginia

F. B. HUTT
Department of Poultry Husbandry
Cornell University
Ithaca, New York

SAMUEL HYMAN, M.D.
55 East Washington Street
Chicago, Illinois

T. H. INGALLS, M.D.
Department of Epidemiology
Harvard Medical School
695 Huntington Avenue
Boston 15, Massachusetts

M. R. IRWIN
Department of Genetics
University of Wisconsin
Madison, Wisconsin

S. LEON ISRAEL, M.D.
2116 Spruce Street
Philadelphia 3, Pennsylvania

H. A. ITANO
4819 Flanders Avenue
Kensington, Maryland

HARRY A. JANKIEWICZ
1320 E. Windsor Road
Glendale 5, California

GEORGE JAY
Geneticist,
Laboratory Aids Branch
National Institutes of Health
Bethesda 14, Maryland

J. A. JENKINS
Division of Genetics
314 Hilgard Hall
University of California
Berkeley 4, California

GEORGE A. JERVIS, M.D.
Thiells
New York

OLA JOHNSTON
1801 West Mulberry Street
Denton, Texas

D. H. JOLLY, M.D.
Box 144
Wrentham, Mass.

BONNIE M. JONES (MRS.)
Department of Anthropology
University of Arizona
Tucson, Arizona

SISTER TERRESITA JUDD
Biology Department
College of St. Catherine
St. Paul, Minnesota

C. W. JUNGEBLUT, M.D.
630 West 168th Street
Columbia Medical Center
Department of Bacteriology
New York City, New York

L. B. KALINOWSKY, M.D.
115 East 82nd Street
New York 28, New York

FRANZ J. KALLMAN, M.D.
722 West 168th Street
New York State Psychiatric Institute
New York 32, New York

HAROLD KALTER
Dept. of Genetics
McGill University
Montreal, P.Q.,
Canada

A. R. KAPLAN
Zoology Department
University of Texas
Austin 12, Texas

BENJAMIN KARPMAN, M.D.
4419 42nd Street
Washington, D. C.

MARY M. KEEFE
315 Thayer St.
Providence, R. I.

C. E. KEELER
Georgia State College for Women
Milledgeville, Georgia

W. R. KEELER, M.D.
The Hospital for Sick Children
555 University Avenue
Toronto 2, Ontario
Canada

ROGER F. KELLER
Dept. of Biology
University of Akron
Akron, Ohio

OSCAR KEMPTHORNE
Statistical Laboratory
Iowa State College
Ames, Iowa

A. T. KENYON, M.D.
Department of Medicine
University of Chicago
Chicago 37, Illinois

WALTER KENYON
1650 Hewitt Avenue
St. Paul 4, Minnesota

ELLIS R. KERLEY
Heredity Clinic
University of Michigan
Ann Arbor, Mich.

JAMES KING, M.D.
Firmin Desloge Hospital
1325 S. Grand Avenue
St. Louis 4, Missouri

ALFRED C. KINSEY
Institute for Sex Research
Indiana University
Bloomington, Indiana

LT. (J.G.) IRVIN KLEIN, U.S.N.
Staff of Commander Service Squadron One
% Fleet Post Office
San Francisco, California

H. W. KLOEPFER
Associate Professor of Anatomy
Tulane University School of Medicine
New Orleans 18, La.

EMANUEL KLOSK, M.D.
46 Lyons Avenue
Newark, New Jersey

C. K. KLUCKHOHN
Russian Research Center
Harvard University
16 Dunster Street
Cambridge 38, Mass

H. KLUVER
Culver Hall
University of Chicago
Chicago 37, Illinois

BERTRAM S. KRAUS
Department of Anthropology
University of Arizona
Tucson, Arizona

ROBERT S. KROOTH
5029 N. Winthrop Avenue
Chicago 40, Illinois

ERNEST H. KUSCH, M.D.
Wards Island
New York 35, New York

H. B. LANG, M.D.
678 Madison Avenue
Albany, N. Y.

PAUL N. LARSEN, M.D.
1133 Punchbowl Avenue
Honolulu, Hawaii

K. S. LASHLEY
Yerkes Laboratories
Orange Park, Florida

GABRIEL W. LASKER
21 F University Houses
Eagle Heights
Madison 5, Wisconsin

MARGARET W. LASKER
64 Shelley Avenue
Yonkers 2, New York

W. S. LAUGHLIN
Department of Anthropology
University of Oregon
Eugene, Oregon

H. LEFKOE, M.D.
Meeting House & Kingsley Roads
Jenkintown, Pennsylvania

W. G. LENNOX, M.D.
47 Dudley Road
Newton Center 59, Massachusetts

E. B. LESSER
Castle Point
Hoboken, New Jersey

H. LEVENE
22 East 88th Street
New York 28, New York

LENA LEVINE, M.D.
30 Fifth Avenue
New York City, New York

PHILIP LEVINE, M.D.
Ortho Research Foundation
Raritan, New Jersey

VICTOR E. LEVINE, M.D.
Creighton University School of Medicine
Omaha 2, Nebraska

M. LEVITAN
Department of Biology
Virginia Polytechnic Institute
Blacksburg, Virginia

DANIEL F. LEVY, M.D.
1288 Chapel Street
New Haven, Connecticut

NOLAN D. C. LEWIS, M.D.
New Jersey Neuropsychiatric Institute
Skillman, New Jersey

C. C. LI
School of Public Health
University of Pittsburgh
Pittsburgh 13, Pennsylvania

A. M. LILIENFELD
Dept. of Epidemiology
School of Hygiene
Johns Hopkins University
Baltimore 5, Maryland

OLIVE M. LOMBARD (MISS)
47 Charlotte Road
Newton Centre 59, Massachusetts

ALMA W. LOONEY (MRS.)
50 Winans Drive
Yonkers, N. Y.

ALBERT A. LORENZ
515 S. Barstow Street
Eau Claire, Wisconsin

MAX B. LURIE, M.D.
The Henry Phipps Institute
The University of Pennsylvania
Seventh & Lombard Streets
Philadelphia 47, Pennsylvania

JAY L. LUSH
Curtiss Hall
Iowa State College
Ames, Iowa

EATON M. MCKAY, M.D.
133 South Lasky Drive
Beverly Hills, California

MADGE T. MACKLIN, M.D.
Room 122 B
Starling Loving Hall
Ohio State University
Columbus 10, Ohio

HULDA MAGALHAES
R.F.D.
Hopewell, New Jersey

BENJAMIN MALZBERG
New York State Dept. of Mental Higiene
State Office Building
Albany, New York

ALBERT MARTIN, JR., M.D.
1155 Murrayhill Avenue
Pittsburgh 17, Pennsylvania

ALFRED B. MASON, M.D.
Preventive Medicine Unit #3
Camp Lejeune, N. C.

G. A. MATSON
Minneapolis War Mem. Blood Bank
1914 LaSalle Avenue
Minneapolis 3, Minnesota

THEODORE D. MCGOWN
Department of Anthropology
University of California
Berkeley 4, California

E. S. MCDONOUGH
Biology Department
Marquette University
Milwaukee, Wisconsin

J. CARSON MCGUIRE
Department of Educational Psychology
308 Sutton Hall
University of Texas
Austin, Texas

VICTOR A. MCKUSICK
Johns Hopkins Hospital
Baltimore 5, Maryland

WALLACE MCNUTT
Department of Anatomy
University of Texas Medical Branch
Galveston, Texas

WILLIAM C. MELOY
2019 R St. N.W.
Washington 9, D. C.

D. J. MERRELL
Department of Zoology
University of Minnesota
Minneapolis 14, Minnesota

H. HOUSTON MERRITT, M.D.
710 West 168th Street
New York 32, New York

J. D. METRAKOS
McGill University
Department of Genetics
Biology Building
Montreal, Canada

HARVEY L. MEYERS
701 Cherry Lane
East Lansing, Michigan

STANLEY N. MEYERS
6620 N. Seeley Avenue
Chicago 45, Ill.

G. H. MICKEY
Department of Biological Sciences
Northwestern University
Evanston, Illinois

H. L. MICKLEWRIGHT
Department of Zoology
University of Arizona
Tucson, Arizona

AUSTIN R. MIDDLETON
Department of Biology
University of Louisville
Louisville 8, Kentucky

CHARLES MIDLO, M.D.
1404 Louisiana Avenue
New Orleans 15, Louisiana

ROBERT A. MILCH, M.D.
Peter Bent Brigham Hospital
721 Huntington Avenue
Boston 15, Massachusetts

DWIGHT D. MILLER
Dept. of Zoology
University of Nebraska
Lincoln 8, Nebraska

JAMES R. MILLER
78 Harvard Avenue
Toronto, Canada

D. E. MINNICH
Department of Zoology
University of Minnesota
Minneapolis 14, Minnesota

MAURICE L. MOORE
Vick Chemical Co.
122 East 42nd Street
New York 17, New York

ROBERT F. MOORE, M.D.
Boston Psychopathic Hospital
Boston 15, Massachusetts

RAY MOREE
Zoology Department
State College of Washington
Pullman, Washington

H. J. MULLER
5203 Pilikai Street
Honolulu, Hawaii

DOUGLAS POWER MURPHY, M.D.
301 S. Bowman Avenue
Merion Station, Pennsylvania

GARDNER MURPHY
Menninger Foundation
Topeka, Kansas

N. MYRIANTHOPOULOS
Dight Institute
University of Minnesota
Minneapolis 14, Minnesota

GEORGE W. NACE
2402 Chapel Hill Road
Durham, North Carolina

J. V. NEEL, M.D.
Heredity Clinic
University of Michigan
Ann Arbor, Michigan

MARQUE O. NELSON, M.D.
510 Medical Arts Building
Tulsa, Oklahoma

R. W. NEWMAN
EPD, QMR & D Center
Natick, Massachusetts

E. F. NORELIUS (MRS.)
110 S. Grand Ave. W.
Springfield, Illinois

HORACE W. NORTON
University of Illinois
Urbana, Illinois

DOLORES NOURSE
The Iraq Museum
Baghdad, Iraq

EUGENE F. OAKBERG
Oak Ridge National Laboratory
P. O. Box P
Oak Ridge, Tennessee

ANGELINE O'DONNELL, M.D.
Cleveland Receiving Hospital
3395 Scranton Road
Cleveland, Ohio

CLARENCE P. OLIVER
Department of Zoology
University of Texas
Austin, Texas

JOSEPH G. O'MARA
Genetics Department
Iowa State College
Ames, Iowa

FREDERICK OSBORN
230 Park Avenue
New York City, New York

R. H. OSBORNE
Constitution Clinic
620 W. 168th Street
New York 32, N. Y.

LOUISE F. OVERTON (MRS.)
3319 N. High Street
Columbus, Ohio

J. DANIEL PALM
2733 Fillmore, N. E.
Minneapolis 18, Minnesota

HARRIET HYMAN PARKER
44 Richards Road
Columbus 14, Ohio

G. E. PASTERAK, M.D.
322 Osborn Building
Cleveland 15, Ohio

SIGSMUND PELLER, M.D.
164 East 81st Street
New York City 28, New York

DOROTHY PERMAR
College of Dentistry
Ohio State University
Columbus 10, Ohio

RICHARD E. PETERSON, M.D.
Radioisotope Unit
Veterans Administration Hospital
Iowa City, Iowa

VIRGINIA RAE PHELPS
P. O. Box 522
East Lansing, Michigan

PHOEBE M. PHILLIPS (MISS)
Department of Zoology
University of Texas
Austin 12, Texas

HYMAN I. PILGRIM, M.D.
Cancer Research
Genetics Laboratory
University of California
Berkeley 4, California

HARRIET F. PILPEL (MRS.)
Greenbaum, Wolff & Ernst
285 Madison Avenue
New York 17, New York

GREGORY PINCUS
222 Maple Avenue
Shrewsbury, Massachusetts

HENRY L. PLAINE
Dept. of Zoology and Entomology
Ohio State University
Columbus 10, Ohio

KAREL PLANANSKY, M.D.
Veterans Administration Hospital
Canandaigua, N. Y.

HAROLD H. PLOUGH
Biological Laboratory
Amherst College
Amherst, Massachusetts

WILLIAM S. POLLITZER
Institute for the Study of Human Variation
413 West 117th St.
New York, N. Y.

W. T. POMMERENKE, M.D.
School of Medicine & Dentistry
260 Crittenden Boulevard
Rochester 20, New York

PAUL POPENOE
2503 North Marengo Avenue
Altadena, California

ADOLPH POSNER, M.D.
667 Madison Avenue
New York 21, N. Y.

E. J. POTCHEN
13648 Ironwood Drive
Marne, Michigan

EDITH L. POTTER, M.D.
Chicago Lying-in Hospital
5841 Maryland Avenue
Chicago 37, Illinois

E. L. POWERS
Argonne National Laboratory
P. O. Box 299
Lemont, Illinois

EDWARD L. PRATT, M.D.
Department of Pediatrics
Southwestern Medical School
2211 Oak Lawn Avenue
Dallas 19, Texas

BRONSON PRICE
Apt. B-1
2617 Southern Avenue, S. E.
Washington 20, D. C.

RUTH R. PUFFER
Pan American Sanitary Bureau
Washington, D. C.

S. RADO, M.D.
25 East 86th Street
New York 28, New York

JOHN D. RAINER
2 Fisher Drive
Mt. Vernon, N. Y.

A. E. RAKOFF, M.D.
Spruce Medical Building 3rd Floor
269 South 19th Street
Philadelphia, Pennsylvania

HELEN M. RANNEY (M.D.)
Harkness Pavilion
180 Fort Washington Ave.
New York 32, N. Y.

IONEL RAPAPORT (M.D.)
Wisconsin Psychiatric Inst.
1552 University Ave.
Madison, Wisconsin

MILTON RAPOPORT, M.D.
6520 Wissahickon Avenue
Philadelphia 19, Pennsylvania

HENRY EARL RATH
Iowa State Teachers College
Cedar Falls, Iowa

HAROLD RAUCH
Department of Zoology
University of Massachusetts
Amherst, Massachusetts

LEONARD J. RAVIZ, M.D.
Waukegan Hotel #1215
4 North Sheridan Road
Waukegan, Illinois

C. A. REED
College of Pharmacy
University of Illinois
808 South Wood Street
Chicago 12, Illinois

ERNEST REED
204 Crawford Avenue
Syracuse 10, New York

S. C. REED
Dight Institute for Human Genetics
University of Minnesota
Minneapolis 14, Minnesota

T. EDWARD REED
Institute of Human Biology
University of Michigan
Ann Arbor, Michigan

D. B. W. REID, M.D.
Connaught Medical Research Laboratories
University of Toronto
Toronto, Ontario, Canada

D. E. REID, M.D.
221 Longwood Avenue
Boston, Massachusetts

DAVID REISNER, M.D.
114 East 61st Street
New York 21, New York

J. PAUL REYNOLDS
Zoology Department
Florida State University
Tallahassee, Florida

MRS. EDYTHE T. RICHARDSON
104 Nesmith Hall
Durham, New Hampshire

D. C. RIFE
Institute of Genetics
Ohio State University
Columbus, Ohio

S. A. RIFENBURGH
Biology Annex
Purdue University
West Lafayette, Indiana

H. P. RILEY
Department of Botany
University of Kentucky
Lexington 29, Kentucky

E. W. ROBBINS, M.D.
1203 E. Columbia Ave.
Philadelphia 25, Pennsylvania

ELMER ROBERTS
College of Agriculture
University of Illinois
Urbana, Illinois

D. W. ROBERTSON
Head, Agronomy Department
Colorado A & M College
Fort Collins, Colorado

G. Gordon Robertson
Division of Anatomy
University of Tennessee
Memphis 3, Tennessee

Gladys C. Robinson
6638 S. Drexel Avenue
Chicago 37, Illinois

Richard L. Rosenfield, M.D.
51 East 90th Street
New York 28, New York

John B. Ross, M.D.
Jacksonville Blood Bank, Inc.
536 West Tenth Street
Jacksonville, Florida

Jacques Rousseau
Jardin Botanique de Montreal
4101 est, rue Sherbrooke
Montreal 36, P. Q., Canada

E. M. Royer
926 North Avon
Dallas, Texas

G. M. Ruckerbauer (Miss)
Department of Zoology
University of Toronto
Toronto 5, Ontario

Evelyn H. Russell (Mrs.)
77 N. Whitney Street
Amherst, Mass.

W. L. Russell
Biology Division
Oak Ridge National Laboratory
P. O. Box P
Oak Ridge, Tennessee

Monte Salvin, M.D.
1921 Wilshire Boulevard
Los Angeles 5, California

Diane Sank (Miss)
Dept. of Medical Genetics
722 West 168th Street
New York 32, New York

J. A. Saxton, Jr., M.D.
5354 Waterman Avenue
St. Louis 12, Missouri

Amram Scheinfeld
41 Fifth Avenue
14-E
New York 3, N. Y.

William A. Schonfeld, M.D.
2 East 85th Street
New York 28, New York

William J. Schull
Heredity Clinic
1135 East Catherine Street
University of Michigan
Ann Arbor, Michigan

J. W. Schut, M.D.
Galesburg State Research Hospital
Galesburg, Illinois

Gabriel A. Schwarz, M.D.
255 South 17th Street
Philadelphia 3, Pennsylvania

M. D. Schweitzer
134 W 92nd Street
New York 25, N. Y.

J. P. Scott
Box 847 Hamilton Station
Roscoe B. Jackson Memorial Laboratory
Bar Harbor, Maine

Jack Wood Sears
Harding College
Searcy, Arkansas

H. P. G. Seckel, M.D.
6019 Ingleside Avenue
Chicago 37, Illinois

Gabriel Segall, M.D.
1930 Wilshire Blvd.
Los Angeles 5, California

H. L. Shapiro
American Museum of Natural History
Central Park West at 79th St.
New York 24, New York

Emmet E. Shipman
2546 N. Stowell Avenue
Milwaukee 11, Wisconsin

G. J. Siemens
Department of Biology
University of Toledo
Toledo 6, Ohio

Ruth Silberberg, M.D.
Apt. 15-U, The Montclair
18 South Kingshighway
St. Louis 8, Missouri

H. M. Slatis
Department of Genetics
McGill University
Montreal 2, Quebec

Eleanor H. Sliper
Dept. of Zoology
State University of Iowa
Iowa City, Iowa

THORSTEN SMITH, M.D.
615 Rand Street
Chippewa Falls
Wisconsin

RICHARD M. SNODGRASS
Temple University School of Dentistry
Broad and Allegheny Avenues
Philadelphia 40, Pennsylvania

ARTHUR R. SOHVAL
1155 Park Avenue
New York 28, N. Y.

T. M. SONNEBORN
109 Wylie Hall
Indiana University
Bloomington, Indiana

B. P. SONNENBLICK
Rutgers University
40 Rector Street
Newark 2, New Jersey

L. W. SONTAG
Fels Research Institute
Antioch College
Yellow Spring, Ohio

DEAN SPEAR, M.D.
Professional Building
60 South 4th East
Salt Lake City 2, Utah

WARREN P. SPENCER
Dept. of Zoology
University of Texas
Austin 12, Texas

FREDERICK SPERLING
National Institute of Health
Bethesda, Maryland

ROSE SPIEGEL, M.D.
15 W. 84th Street
New York 24, New York

RAMSAY SPILLMAN, M.D.
115 East 61st Street
New York 21, New York

DAVID W. SPRAGUE, M.D.
1417 Marlowe Avenue
Lakewood 7, Ohio

ELIZABETH J. SPRATT
Department of Zoology
University of Toronto
Toronto 5, Canada

JAMES N. SPUHLER
Institute of Human Biology
University of Michigan
Ann Arbor, Michigan

R. E. STAFFORD
Human Engineering Laboratory
2012 DeLancey Place
Philadelphia 3, Pennsylvania

K. F. STEIN
Mount Holyoke College
South Hadley, Massachusetts

A. G. STEINBERG
Children's Cancer Research Found.
The Children's Hospital
300 Longwood Avenue
Boston 15, Mass.

F. E. STEPHENS
Biology 106
University of Utah
Salt Lake City 1, Utah

CURT STERN
Dept. of Zoology
University of California
Berkeley 4, California

KURT STERN, M.D.
2750 West 15th Place
Chicago 8, Illinois

K. A. STILES
Zoology Department
Michigan State College
East Lansing, Michigan

R. STOHLER
1584 Milvia Street
Berkeley 9, California

A. B. STOKES
2 Surrey Place
Toronto, Canada

ABRAHAM STONE, M.D.
40 Park Avenue
New York 16, New York

W. S. STONE
Department of Zoology
University of Texas
Austin 12, Texas

CLYDE STORMONT
School of Veterinary Medicine
University of California
Davis, California

PHILLIP STURGEON, M.D.
Children's Hospital Society
4614 Sunset Boulevard
Los Angeles 27, California

HAZEL SUESSENGUTH (MISS)
Chief, Serology Division
Mount Sinai Hospital
1800 East 105th Street
Cleveland, Ohio

J. H. SUNDER
Addison H. Gibson Laboratory
School of Medicine
University of Pittsburgh
Pittsburgh 13, Pennsylvania

LEON N. SUSSMAN, M.D.
36 East 38th Street
New York 16, New York

H. ELDON SUTTON
Institute of Human Biology
University of Michigan
Ann Arbor, Michigan

LENORE TAYLOR (MISS)
209 Lyman Hall
Syracuse University
Syracuse 10, N. Y.

ROY P. THELANDER
Augsburg College
Minneapolis 4, Minnesota

SYDNEY F. THOMAS, M.D.
Palo Alto Clinic
300 Homer Avenue
Palo Alto, California

MARGARET W. THOMPSON
% J. S. Thompson
Department of Anatomy
University of Alberta
Edmonton, Alberta, Canada

OSCAR L. THOMPSON
Box 177
Bishop College
Marshall, Texas

L. L. THURSTONE
Psychometric Laboratory
University of North Carolina
Chapel Hill, North Carolina

JOHN H. TILDES, M.D.
1417 Marlowe Avenue
Lakewood 7, Ohio

ROBERT L. TIPS, M.D.
Dept. of Bacteriology
University of Texas Medical Branch
Galveston, Texas

HENRY W. TOLL
Counsellor at Law
Equitable Building
Denver, Colorado

HENRY W. TOLL, JR.
1812 High Street
Denver, Colorado

ALLAN TUCKER
Department of Natural Science
Michigan State College
East Lansing, Michigan

J. W. TUKEY
Box 708
Princeton, New Jersey

IRENE AYAKO UCHIDA
Department of Genetics
Hospital for Sick Children
Toronto 2, Ontario, Canada

L. J. UNGER, M.D.
1192 Park Avenue
New York 28, New York

E. L. VAN BUSKIRK, M.D.
308 North 8th Street
Lafayette, Indiana

CAPT. F. D. VAN WART
1517 S. State Street
Ann Arbor, Michigan

VICTOR C. VAUHAN, M.D.
114 W. Coulter St.
Philadelphia 44, Pennsylvania

DONALD G. VERNALL
Institute of Human Biology
University of Michigan
Ann Arbor, Michigan

P. VOGEL, M.D.
51 East 90th Street
New York 28, New York

R. P. WAGNER
Department of Zoology
University of Texas
Austin, Texas

ALLEN A. WALKER
P.O. Box 7252
Portairs Station
Corpus Christi, Texas

BRUCE WALKER
Department of Genetics
McGill University
Montreal, Quebec

NORMA FORD WALKER,
Dept. of Medical Genetics
Hospital for Sick Children
Toronto 2, Canada

HARRY WALLERSTEIN, M.D.
720 Gramatan Avenue
Mt. Vernon, New York

GORDON L. WALLS
School of Optometry
University of California
Berkeley 4, California

MATTHEW WALZER, M.D.
20 Plaza Street
Brooklyn 17, New York

JULIAN E. WARD, M.D.
Chief, EENT Section
Gunter Branch-School of Avn. Med.
Gunter Air Force Base, Alabama

ROBERT WARNER, M.D.
333 Linwood Avenue
Buffalo 9, New York

HERBERT S. WARREN
Hahnemann Medical College
235 North 15th Street
Philadelphia 2, Pennsylvania

KATHERINE BREHME WARREN (MRS.)
Hofstra College
Hempsted, New York

S. L. WASHBURN
Department of Anthropology
University of Chicago
Chicago 37, Illinois

H. M. WATTS, M.D.
194 Princess St.
Lancaster, N.B. Canada

K. H. WEBSTER
601 Sherman Street
Downers Grove, Illinois

ABNER I. WEISMAN, M.D.
1160 Fifth Avenue
New York, New York

EDWARD J. WENSTRUP
Department of Biology
St. Vincent College
Latrobe, Pennsylvania

PAUL WERMER, M.D.
605 East 82nd Street
New York 28, New York

I. B. WEXLER, M.D.
1672 Ocean Avenue
Brooklyn, New York

EDWIN O. WHEELER
Massachusetts General Hospital
Boston 14, Massachusetts

SHIRAS WHITE
Box 285
Princeton, New Jersey

M. WHITTINGHILL
Department of Zoology
University of North Carolina
Chapel Hill, North Carolina

A. E. WIGGAM
340—16th Street
Santa Monica, California

CHAS. R. WILKINSON, JR., M.D.
New York University
Post Graduate Medical School
477 First Avenue
New York 16, New York

S. S. WILKS
Fine Hall
Princeton University
Princeton, New Jersey

ROGER J. WILLIAMS
Chemistry Building 213
University of Texas
Austin 12, Texas

G. B. WILSON
Department of Botany
Michigan State College
East Lansing, Michigan

JAMES G. WILSON, M.D.
Medical School
University of Cincinnati
Cincinnati, Ohio

ALBERT M. WINCHESTER
Stetson University
DeLand, Florida

M. M. WINTROBE, M.D.
175 East 21st South
Salt Lake City, Utah

ERNEST WITEBSKY, M.D.
Dept. of Bacteriology & Immunology
University of Buffalo
24 High Street
Buffalo, New York

IRVING J. WOLMAN, M.D.
Children's Hospital
1740 Bainbridge Street
Philadelphia 46, Pennsylvania

E. H. WOOD, M.D.
120 Genesee Street
Auburn, New York

CHARLES M. WOOLF
Division of Biology
University of Utah
Salt Lake City 1, Utah

GEORGE W. WOOLLEY
Sloan-Kettering Institute
Dept. 136
444 East 68th Street
New York 21, New York

F. H. WRIGHT, M.D.
5739 Kimbark Avenue
Chicago 37, Illinois

J. E. WRIGHT, JR.
Botany Department
Pennsylvania State College
State College, Pennsylvania

SEWALL WRIGHT
Department of Zoology
University of Chicago
Chicago 37, Illinois

FREDERICK D. ZEMAN, M.D.
111 East 88th Street
New York 28, New York

NANCY KENT ZIEBUR (MRS.)
179 E. Pacemont Road
Columbus 2, Ohio

JOSEPH ZUBIN, M.D.
722 West 168th Street
New York 32, New York

ASSOCIATE MEMBERS

JOHN M. ASKEY, M.D.
1930 Wilshire Blvd. Suite 902
Los Angeles 5, California

G. S. BAROFF
1731 Harrison Avenue
Bronx 53, New York

G. P. CHILD, M.D.
128 E. Grant Avenue
Roselle Park
New Jersey

D. M. DEARDEN
General College
Nicholson Hall
University of Minnesota
Minneapolis 14, Minnesota

PHYLLIS H. DEUTSCH (MISS)
163-11 27th Avenue
Flushing, New York

CHARLES EHRET
P. O. Box 299
Argonne National Laboratory
Lamont, Illinois

LESTER FUHRMAN
Tomorrow's Heirlooms
134 Liberty Street
New York 6, New York

CHARLOTTE GERMAN (MRS.)
211 Fort Washington Avenue
New York 32, New York

WILLOUGHBY GOODSMITH
Dept. of Zoology
University of California
Los Angeles 24, California

HELLY KALLMANN, (MRS.)
New York State Psychiatric Inst.
722 West 168th Street
New York 32, N. Y.

ADELBERT A. KOSTENSKY
9700 Hilgert Drive
Cleveland 4, Ohio

HANS LEHFELDT, M.D.
784 Park Avenue
New York 21, New York

F. J. MILLEN
3932 North Farwell Avenue
Milwaukee 11, Wisconsin

N. S. MOORE, M.D.
512 East State Street
Ithaca, New York

J. G. ROBERTSON
Dept. of Zoology
University of British Columbia
Vancouver, B.C., Canada

A. Arthur Roth, M.D.
427 Osborn Building
Cleveland 15, Ohio

Liane Brauch Russell
Biology Division
Oak Ridge National Laboratory
P. O. Box P
Oak Ridge, Tennessee

Morton Schillinger
220 West 98th Street
New York 24, New York

Martin Silberberg, M.D.
18 South Kingshighway
St. Louis 8, Missouri

David E. Soules
Wadley Blood Center
3600 Gaston
Dallas, Texas

Elizabeth Swirnofsky
1832 Anthony Avenue
Bronx 57 New York, New York

Frederick J. Verderosa
527 East Fourth Street
Bloomington, Indiana

Otto A. Wurl, M.D.
Cardiac Laboratory
Massachusetts General Hospital
Boston, Mass.

CORRESPONDING MEMBERS

J. J. Alarez, M.D.
Maximo Gomez 41
Santiago Dominican Republic
West Indies

Julio F. de la Arena
Escuela de Ciencias
Universidad dela Habana
La Habana, Cuba

Claudio Barigozzi
Instituto di Genetica
via Celoria, 10
Milan, Italy

I. R. C. Batchelor, M.D.
151 Morningside Drive
Edinburgh 10, Scotland

P. E. Becker, M.D.
Konigstrasse 18
Tuttlingen, Wurttemberg
Germany

M. Bessis, M.D.
2 rue de Saint-Simon
Paris 7, France

Jan A. Böök, M.D.
State Institute for Race Biology
Uppsala, Sweden

Professor D. E. Breitinger
Anthropologisches Institut der Universität
Franz-Weidenreich-Institut
Senckenberganlage 35
Frankfurt a. M., Germany

J. W. Bruins
Nederlandse Anthropogenetische Vereniging
Gibsonstraat 6
Deventer, Holland

A. Bezerra Coutinho, M.D.
Ave. 17 de Agosto 653
Recife, Pernambuco, Brazil

Marco Fraccaro
Laboratorio di Genetica
Universita di Pavia
Via Forlanini 6
Pavia, Italy

A. Franceschetti, M.D.
3 Avenue de Miremont
Geneva, Switzerland

J. E. Francois, M.D.
Gogheelkundige Klinick
Avenue Pasteur 2
Ghent, Belgium

Newton Freire-Maia
Laboratorio de Genetica
Universidade de Parana
Rua Coronel Dulcidio, 638
Curitiba, Parana
Brazil

Ignazio Gatto, M.D.
Via Pignatelli Aragona 86
Palermo, Sicily, Italy

Luigi Gedda, M.D.
Presso L'Universita di Rome
Largo Amba Aradam 1
Roma, Italy

Alfonso Giordano, M.D.
via Forlanini, 6
University of Pavia
Pavia, Italy

H. GUNTHER
Breiter Weg. 4
Emmendingen
Baden, Germany

P. O. HUBINONT
23 Avenue Ad. Demeur
Brussels, Belgium

L. A. HURST, M.D.
Sterkfontein Hospital
P. O. Box 323
Krugersdorf, Transvaal
South Africa

EIJI INOUYE, M.D
Kogamachi—229
Bunkyo-ku
Tokyo, Japan

RIITI KAWAKAMI, M.D.
Institute of Public Health
Shiba Shirokane Daimachi Mintao-ku
Tokyo, Japan

R. KHERUMIAN
103 rue du Foubourg St. Honore
Paris 8, France

R. L. KIRK
Zoology Dept.
University of Western Australia
Nedlands, Western Australia

PIERRE KISSEL, M.D.
17, Avenue Foch
Nancy (M. & M.)
France

GERHARD KOCH, M.D.
Universitat Nervenklinik
Roxeler Strasse, 131
Munster (Westf.) Germany

TAKU KOMAI
National Institute of Genetics
Misima, Sizuoka-ken
Japan

MAURICE LAMY, M.D.
94 rue de Varenne, VII^{e}
Paris, France

CARL A. LARSON
Genetiska Institutionen
Lunds Universitet
Lund, Sweden

WOLFGANG LEHMAN, M.D.
Roonstrasse, 7
Kiel, Germany

FRITZ G. K. LENZ, M.D.
Wilhelm-Weberstrasse 2
Gottingen
British Zone, Germany

BRIAN MACMAHON
Dept. of Social Medicine
University of Birmingham
Birmingham, England

PIERO MALCOVATI, M.D.
Institute Provinciale di Maternita
Via Palestro 20
Milano, Italy

ISAIAS H. MELSOHN, M.D.
Rua Aurora 880–5
Sao Paulo, Brazil

G. MONTALENTI, M.D.
Instituto di Genetica
Della Universita, Di Napoli
Napoli, Italy

DR. MAYNAHAN
Guy's Hospital
London Bridge, S. E. 1, England

HANS MÜHSAM
27 Ilanot Street
Western Carmel
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